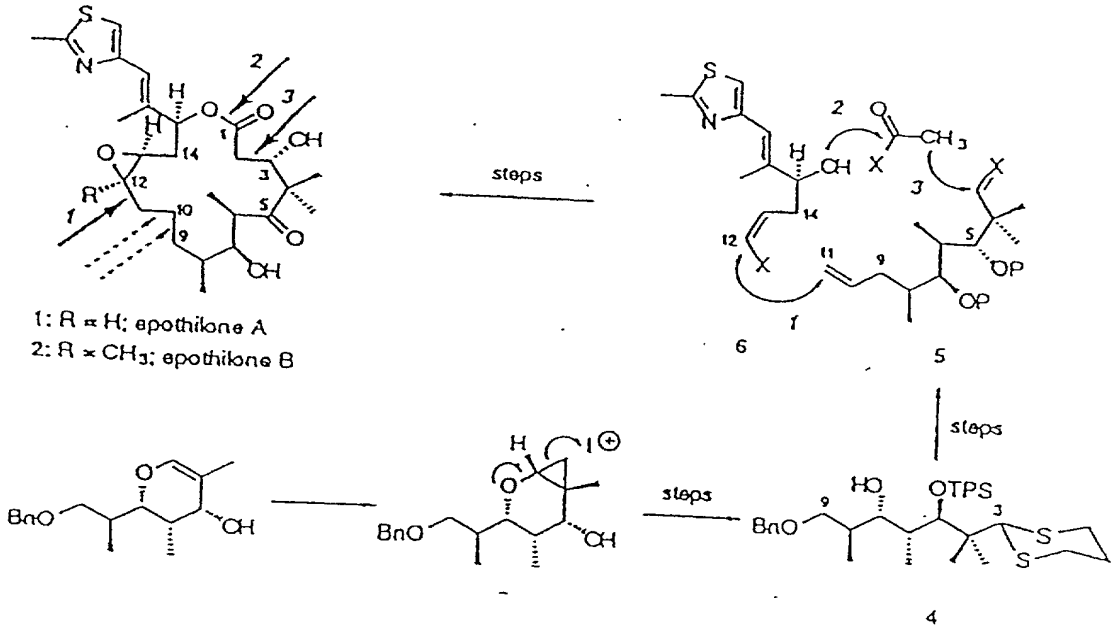
(A)


steps
1: R = H; epothilone A
2: R = CH3; epothilone B
6
5
steps
steps
4

(B)

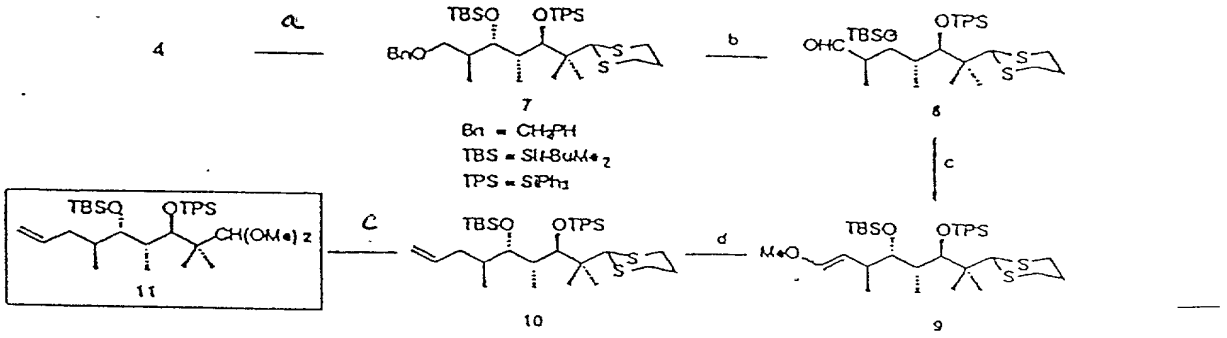

4
a
TBSO
OTPS
BnO
7
Bn = CH2Ph
TBS = SiMe2tBu
TPS = SiPh2
b
OHC
TBSO
OTPS
6
c
TBSO
OTPS
CH(OMe)2
11
C
10
d
MeO
9

Figure 1

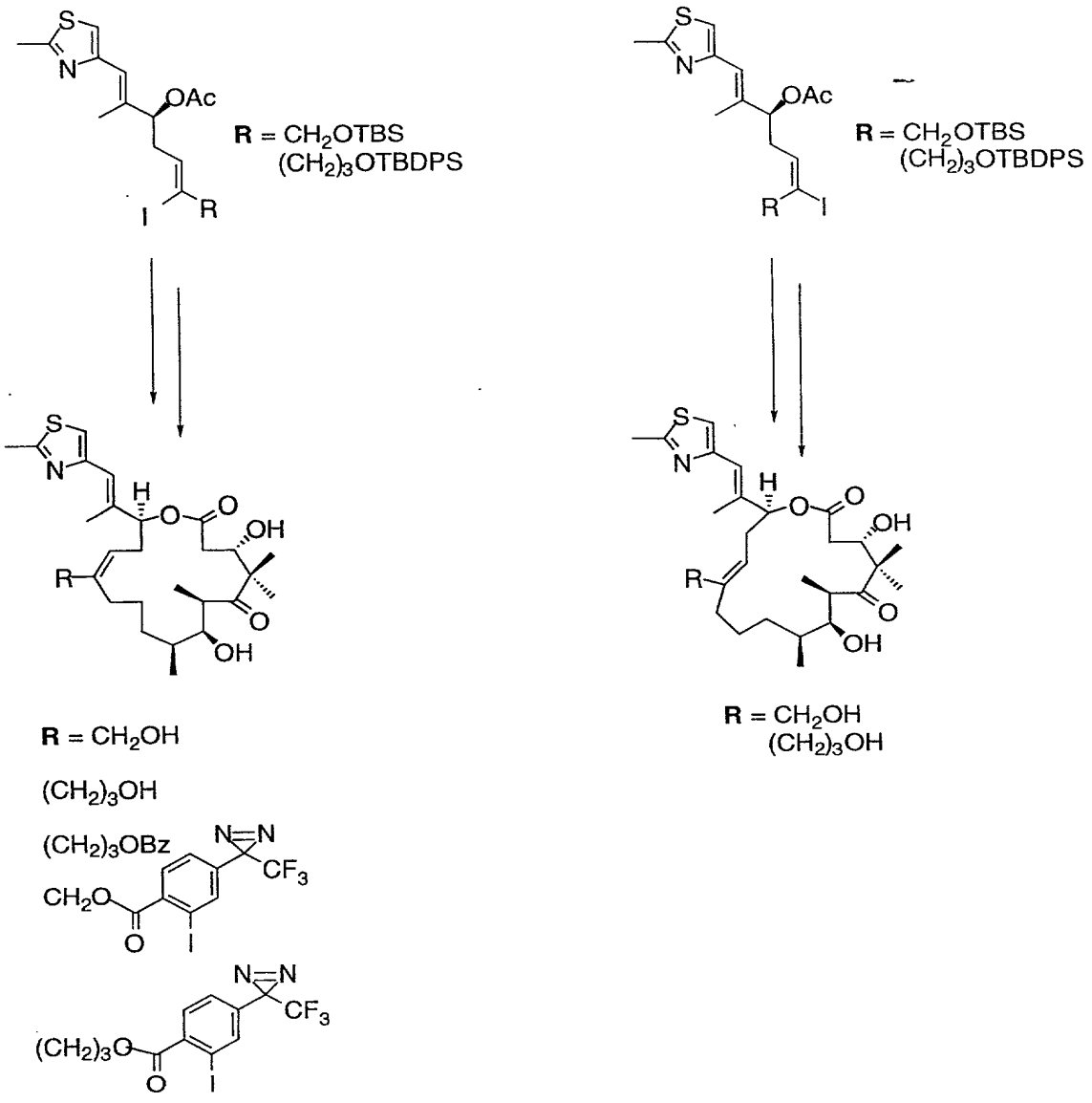

R = CH2OTBS
(CH2)3OTBDPS
R = CH2OTBS
(CH2)3OTBDPS
R = CH2OH
(CH2)3OH
R = CH2OH
(CH2)3OH
(CH2)3OBz
CH2O
CF3
(CH2)3O
CF3

Figure 2

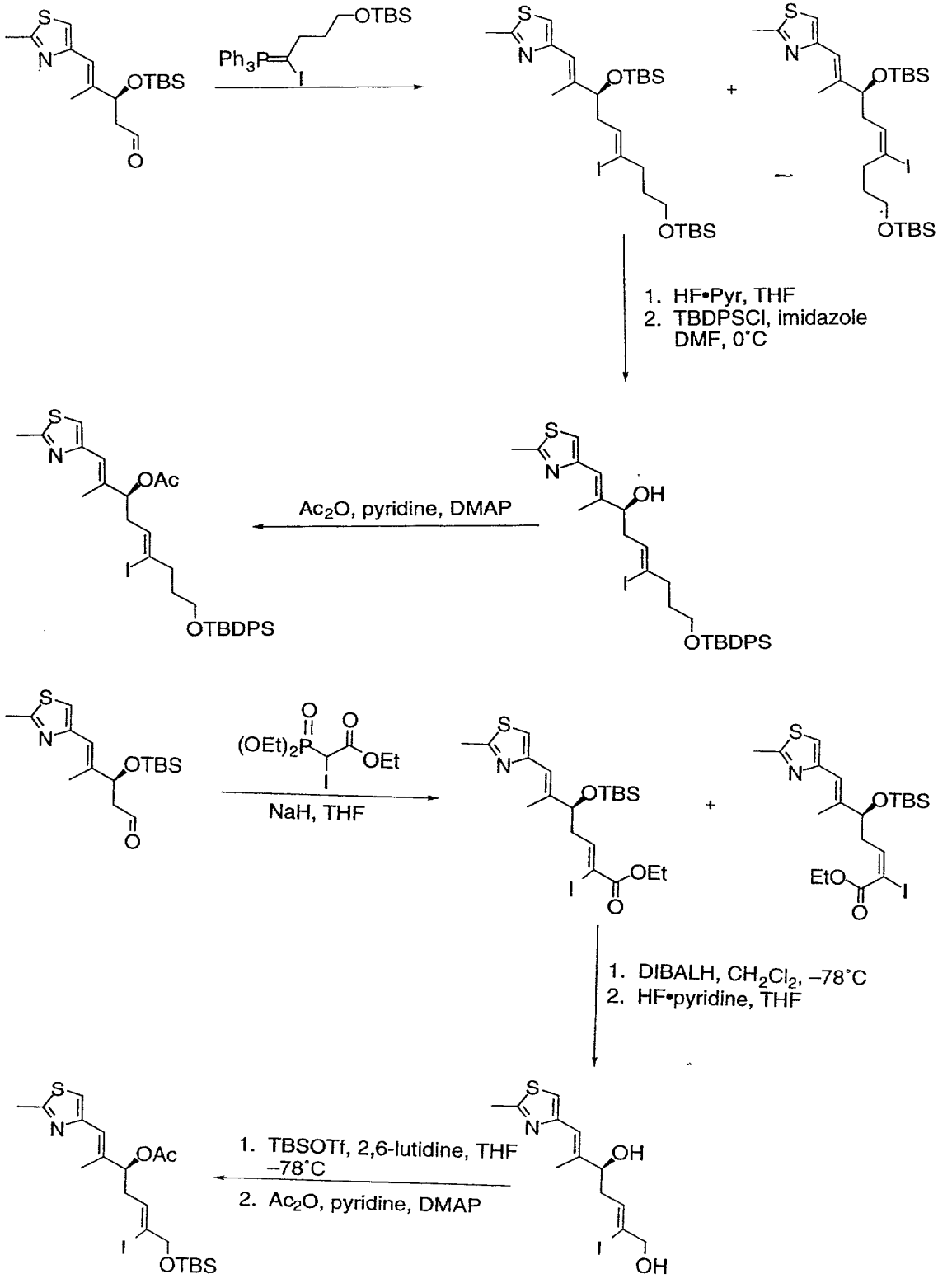

OTBS
Ph3P
I
OTBS
OTBS
OTBS
OTBS
OTBS
1. HF•Pyr, THF
2. TBDPSCl, imidazole
DMF, 0°C
OAc
Ac2O, pyridine, DMAP
OH
OTBDPS
OTBDPS
OTBS
(OEt)2P
O
OEt
NaH, THF
OTBS
OTBS
OEt
EtO
1. DIBALH, CH2Cl2, –78°C
2. HF•pyridine, THF
OAc
1. TBSOTf, 2,6-lutidine, THF
–78°C
2. Ac2O, pyridine, DMAP
OH
OTBS
OH

Figure 3(A)

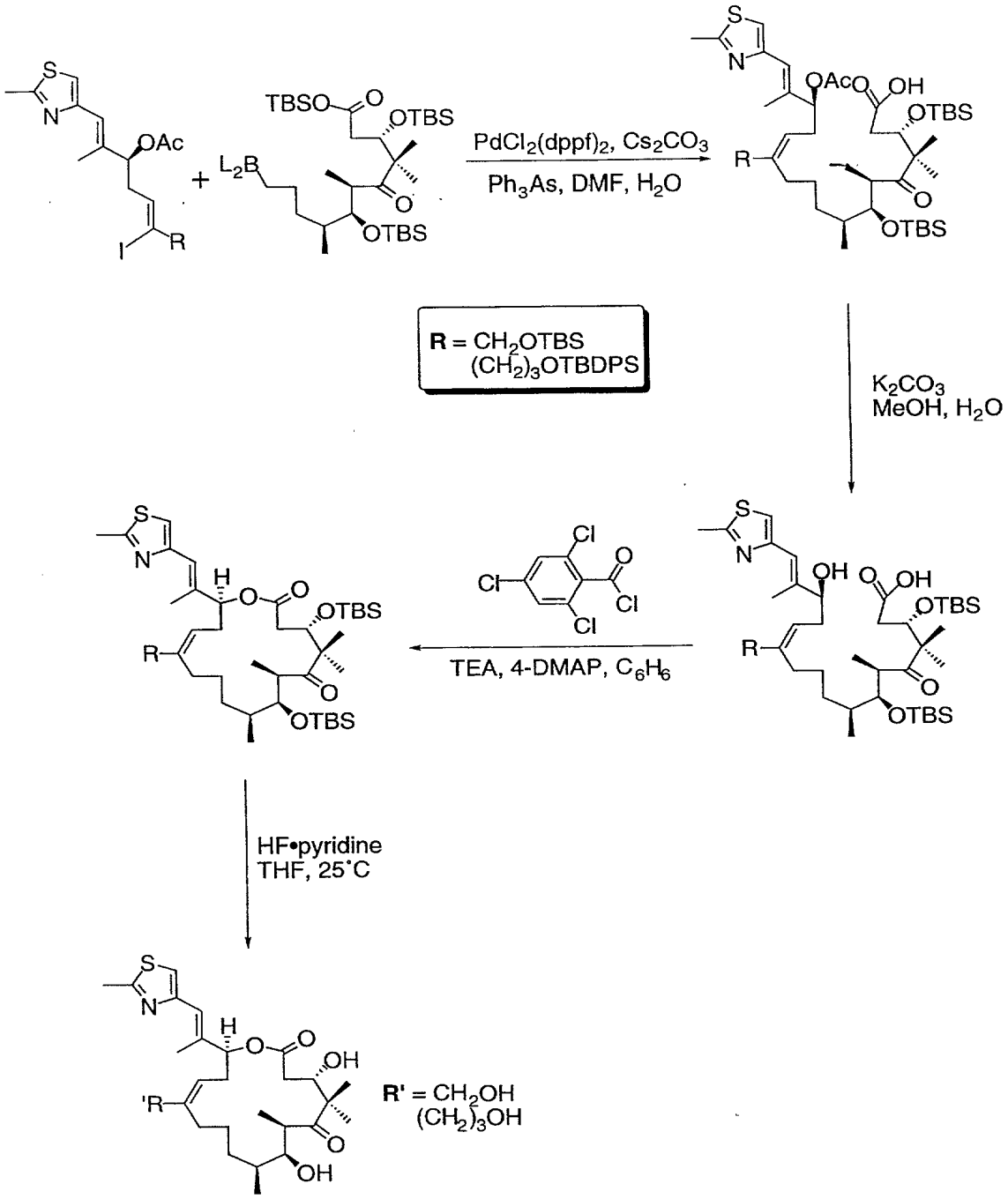
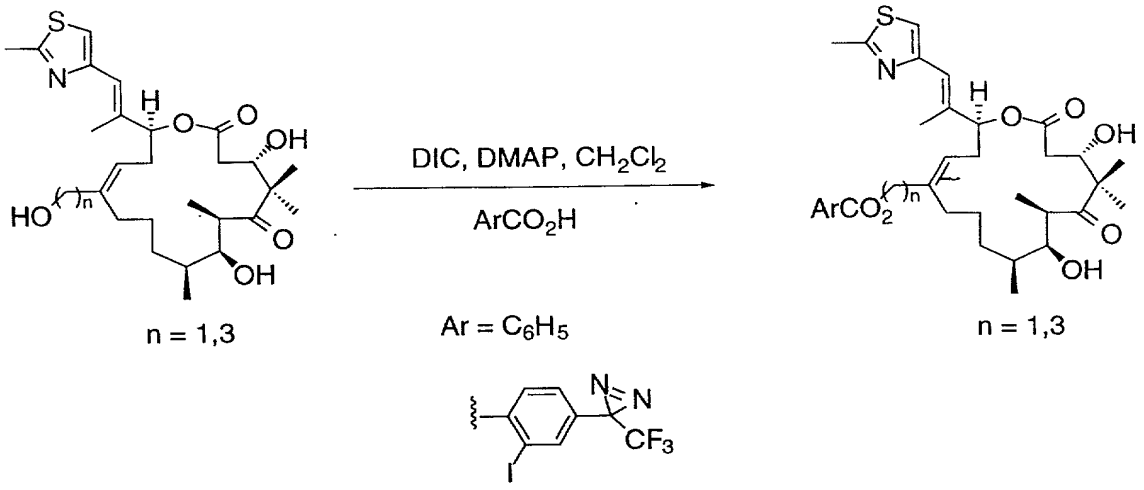

PdCl2(dppf)2, Cs2CO3
Ph3As, DMF, H2O
R = CH2OTBS
(CH2)3OTBDPS
K2CO3
MeOH, H2O
TEA, 4-DMAP, C6H6
HF•pyridine
THF, 25°C
R' = CH2OH
(CH2)3OH

Fig. 3(B)



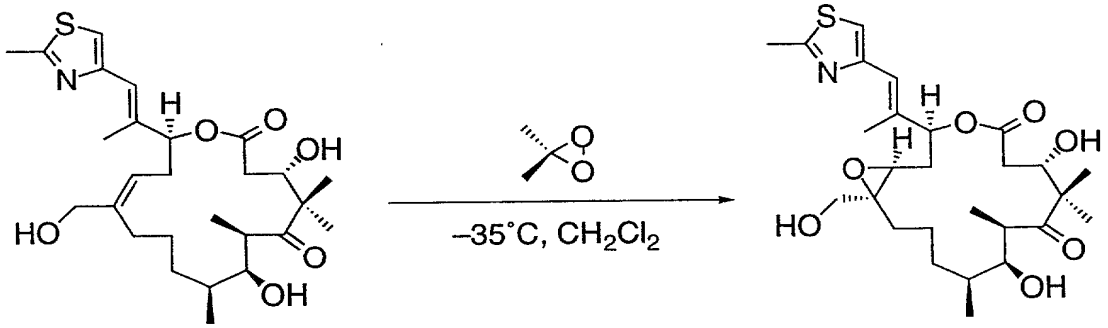


Fig. 3(C)

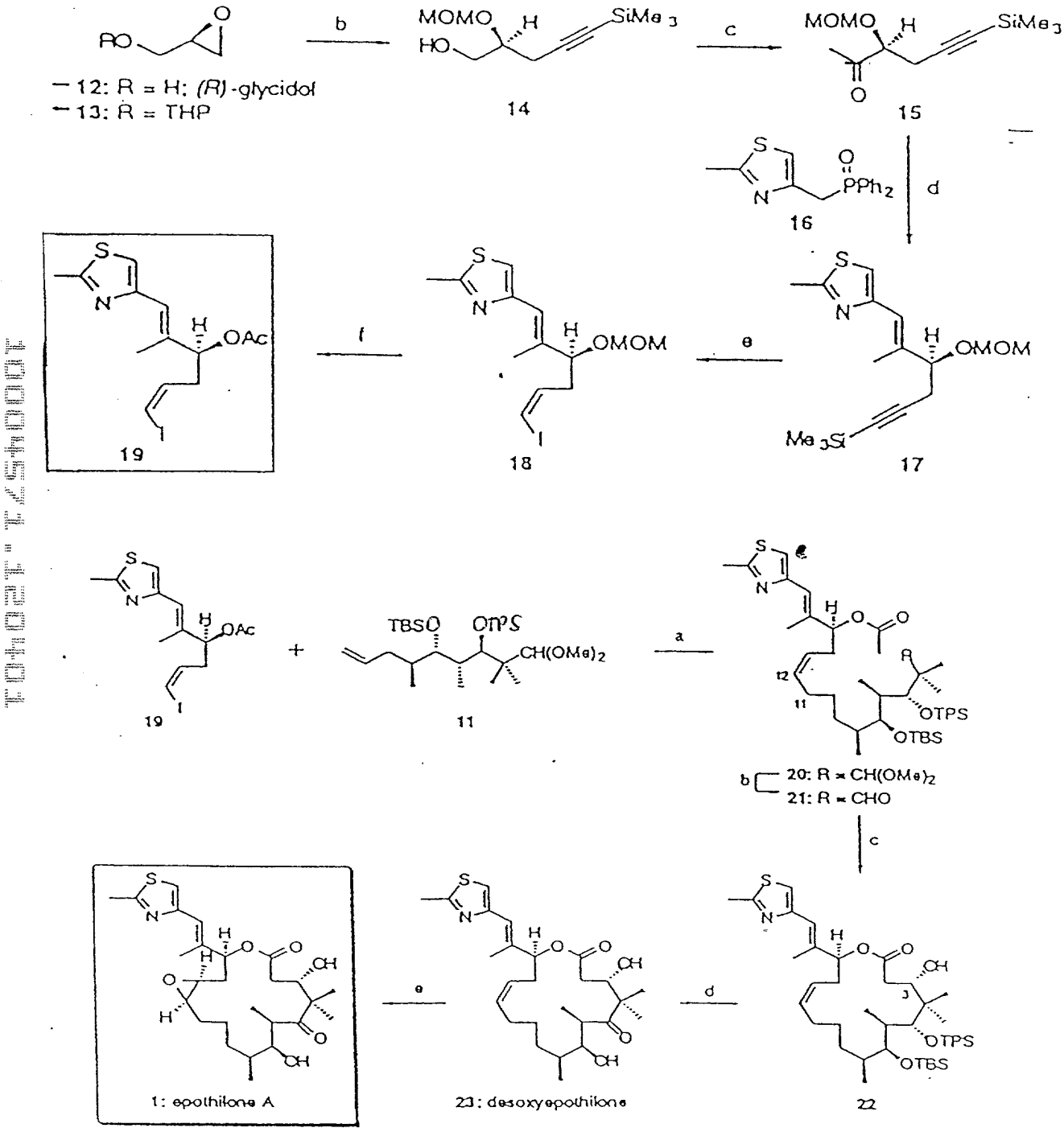

12: R = H; (R)-glycidol
13: R = THP
14
15
16
17
18
19
20: R = CH(OMe)2
21: R = CHO
22
23: desoxyepothilone
1: epothilone A

Figure 4

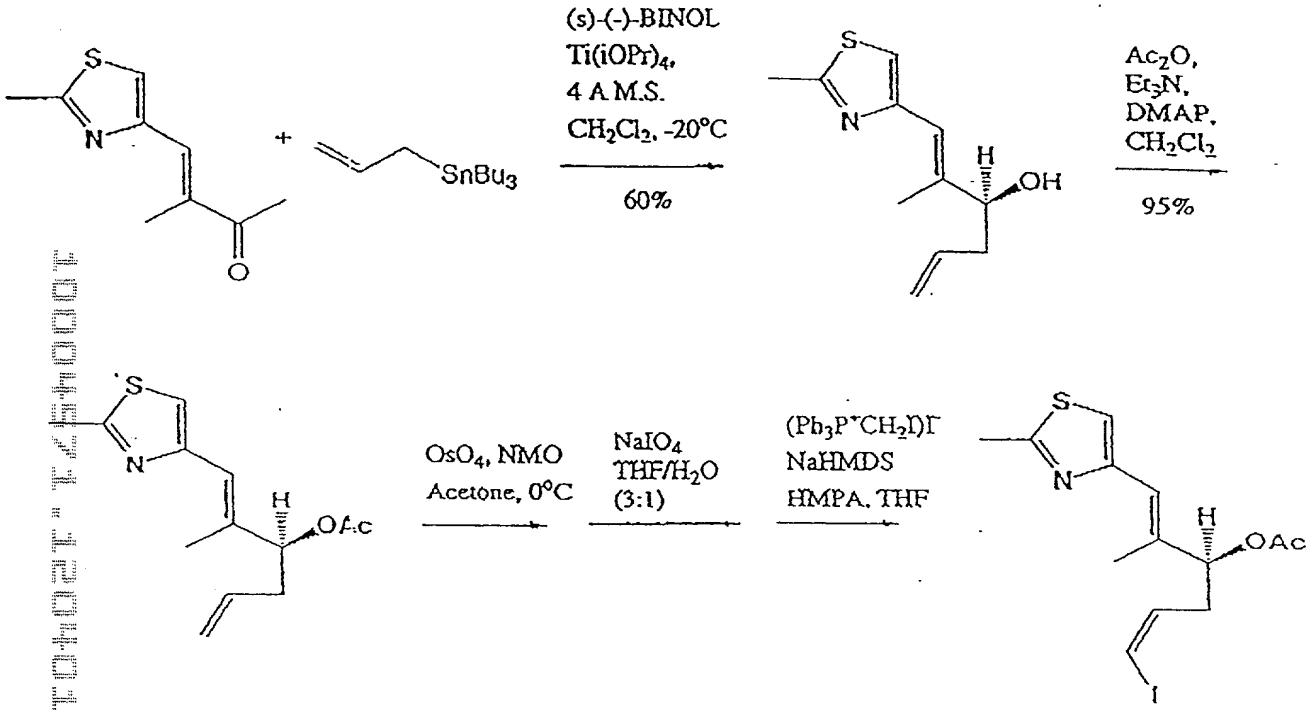
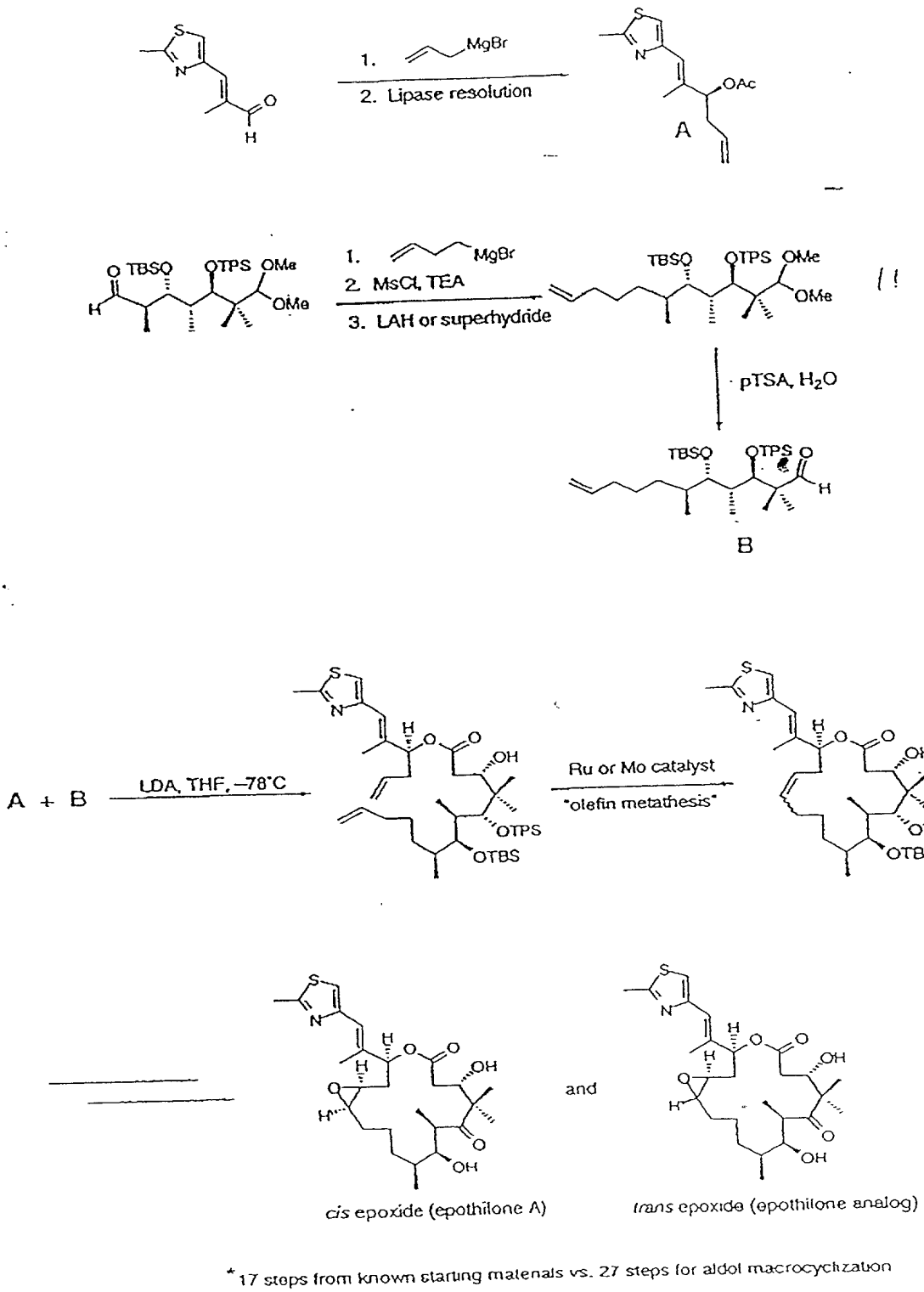
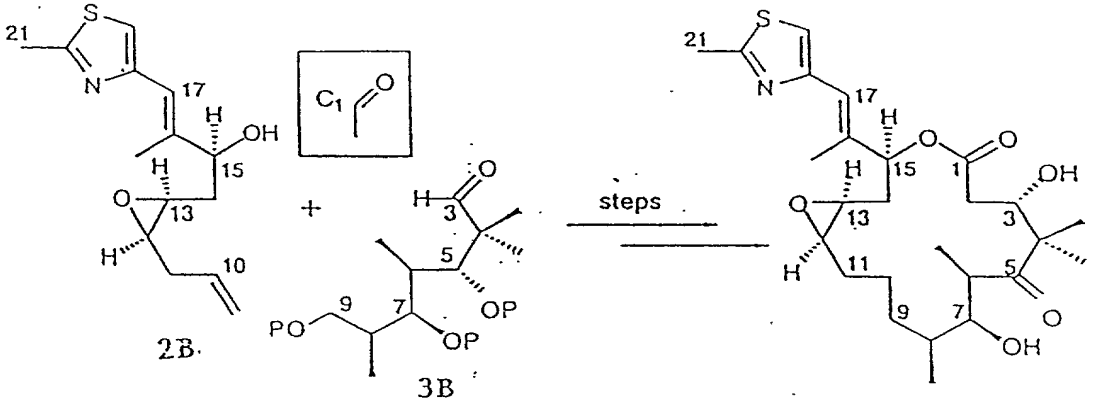

(s)-(-)-BINOL
Ti(iOPr)4,
4 A.M.S.
CH2Cl2, -20°C
60%
Ac2O,
Et3N,
DMAP,
CH2Cl2
95%
OsO4, NMO
Acetone, 0°C
NaIO4
THF/H2O
(3:1)
(Ph3P+CH2I)I-
NaHMDS
HMPA, THF
50% for three steps

Figure 5



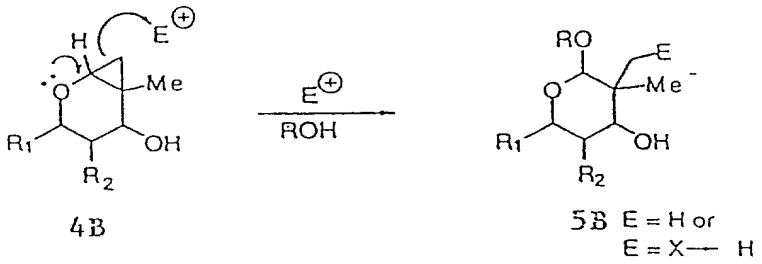
*17 steps from known starting materials vs. 27 steps for aldol macrocyclization

Figure 6



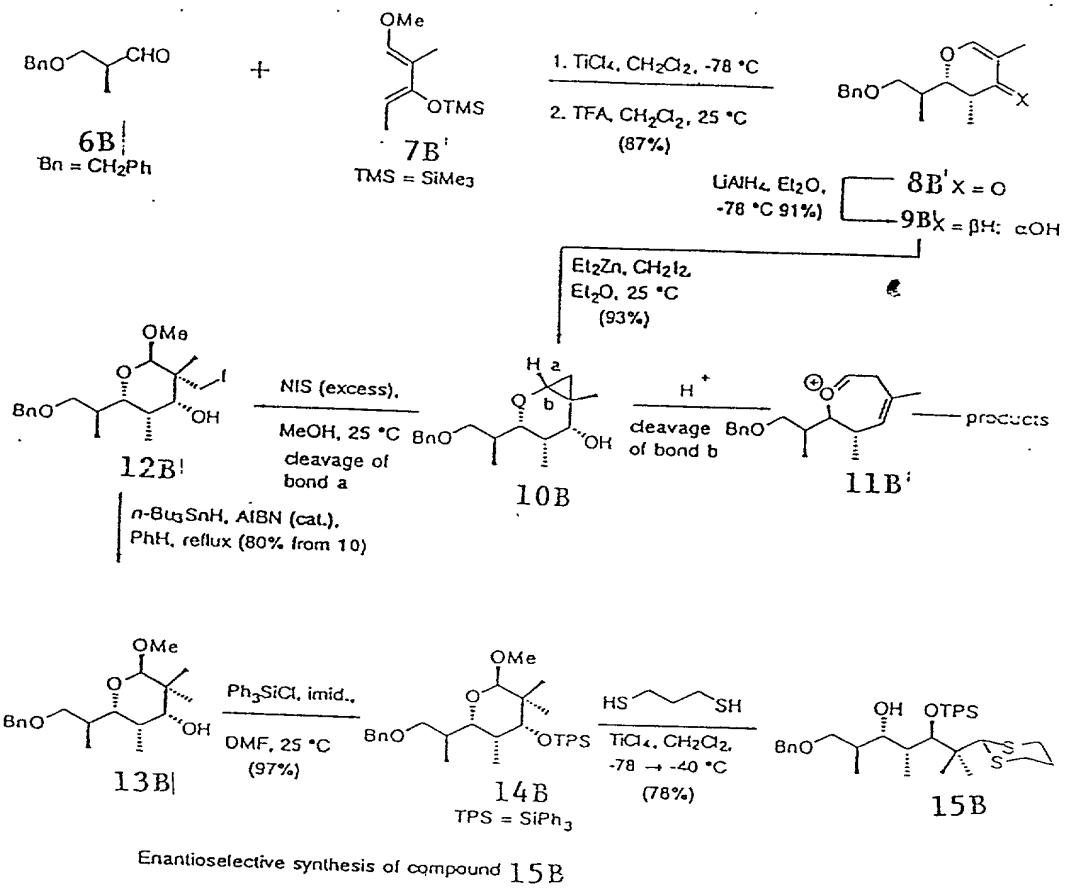
P = unspecified protecting group 1 : epothilone A

Convergent strategy for a total synthesis of epothilone A (1).



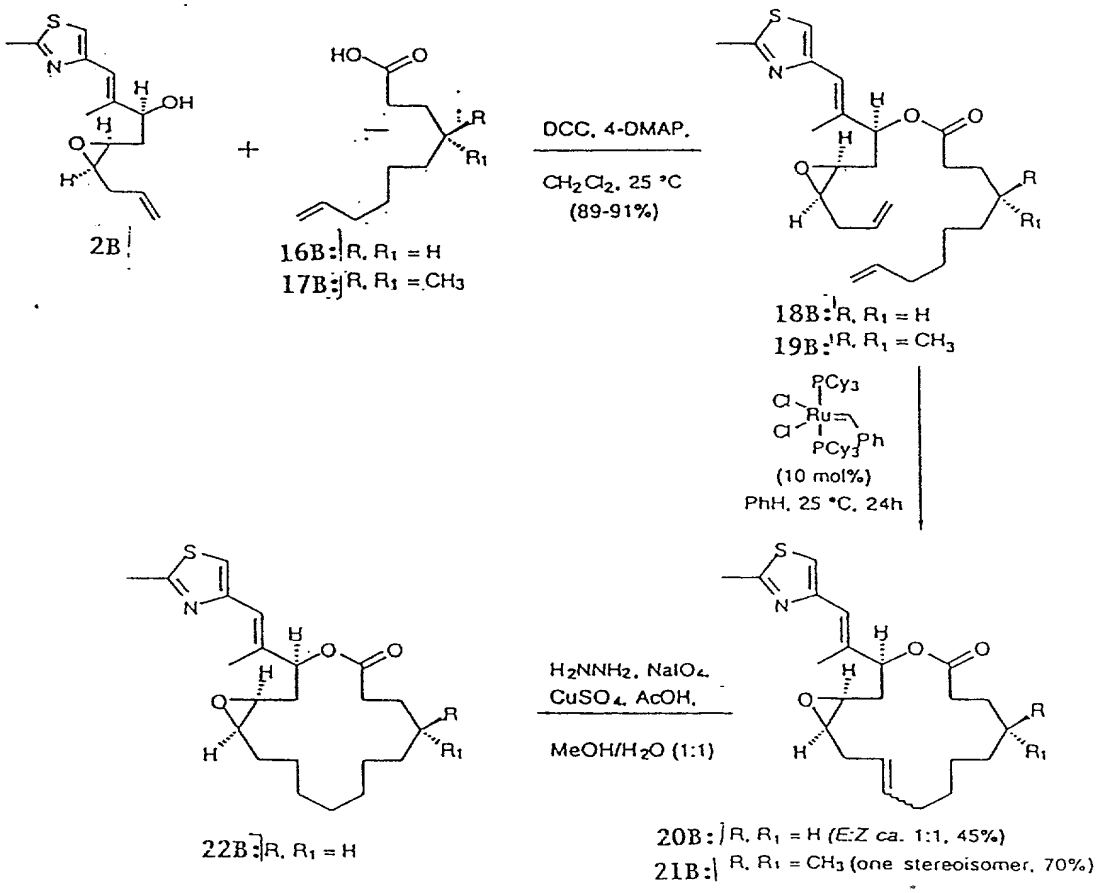
The glycal cyclopropane solvolysis strategy for the introduction of geminal methyl groups.

Figure 7



Enantioselective synthesis of compound 15B

Figure 8



Construction of epothilone model systems 20^B, 21^B, and 22^B by ring-closing olefin metathesis

Figure 9

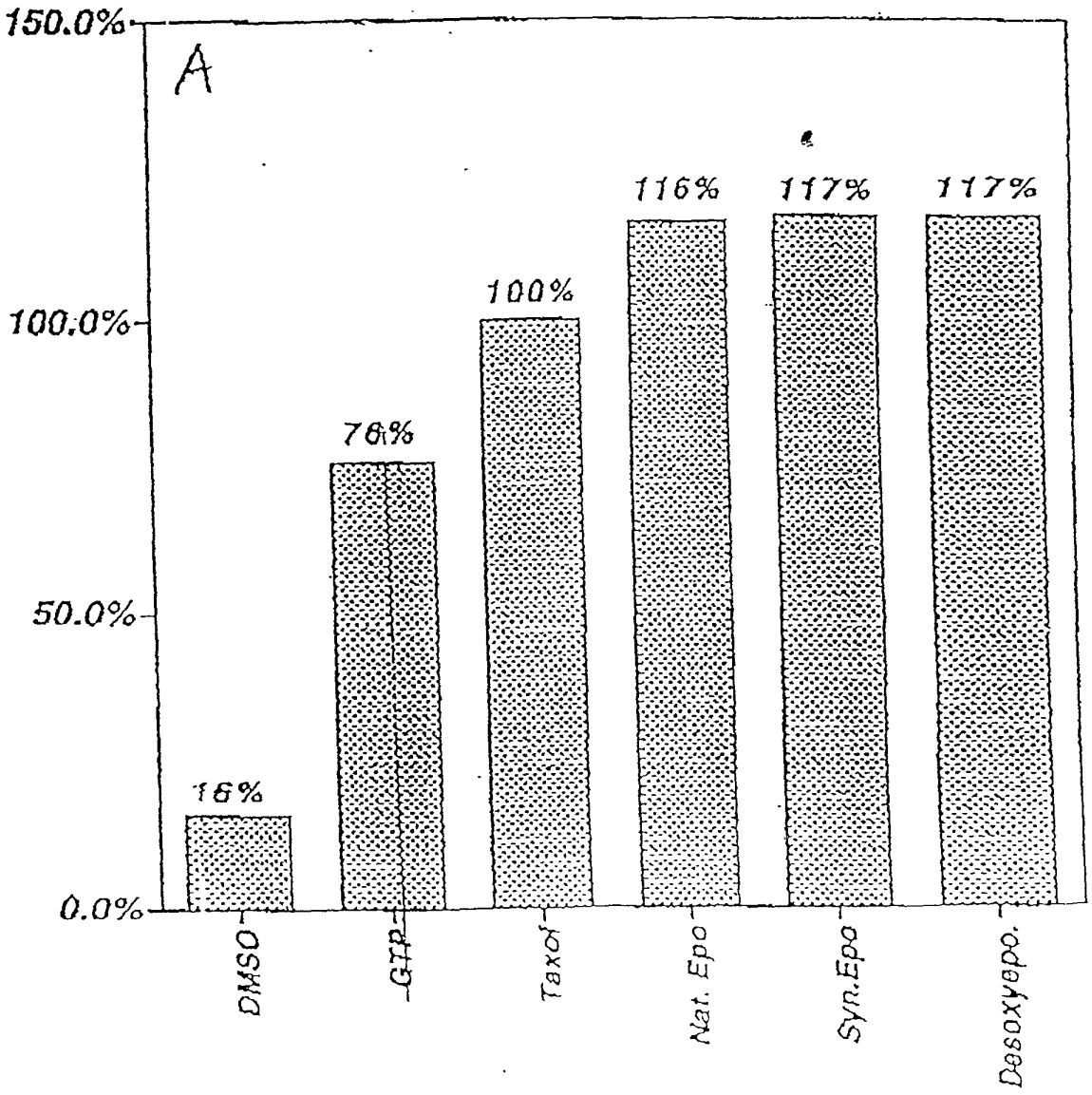

150.0%
100.0%
50.0%
0.0%
A
16%
76%
100%
116%
117%
117%
DMSO
GTP
Taxol
Nat. Epo
Syn.Epo
Desoxyepo.

Figure 10

Patent Application

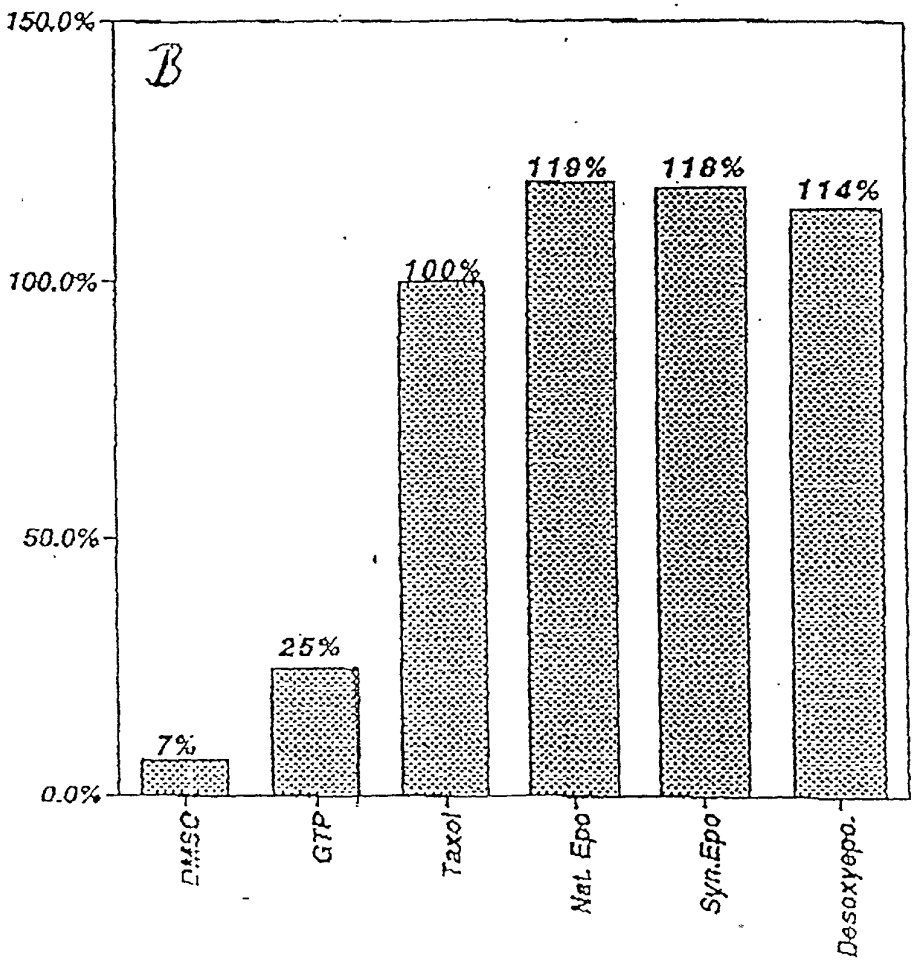
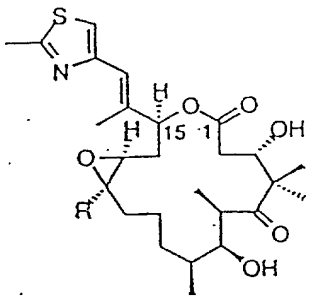


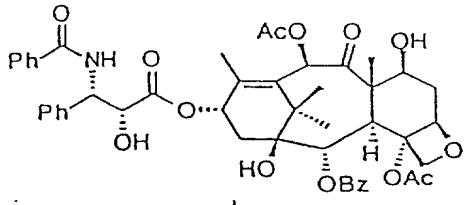
Figure 11

(A)



R = H; epothilone A
R = CH_3; epothilone B

(B)



1A: Taxol™

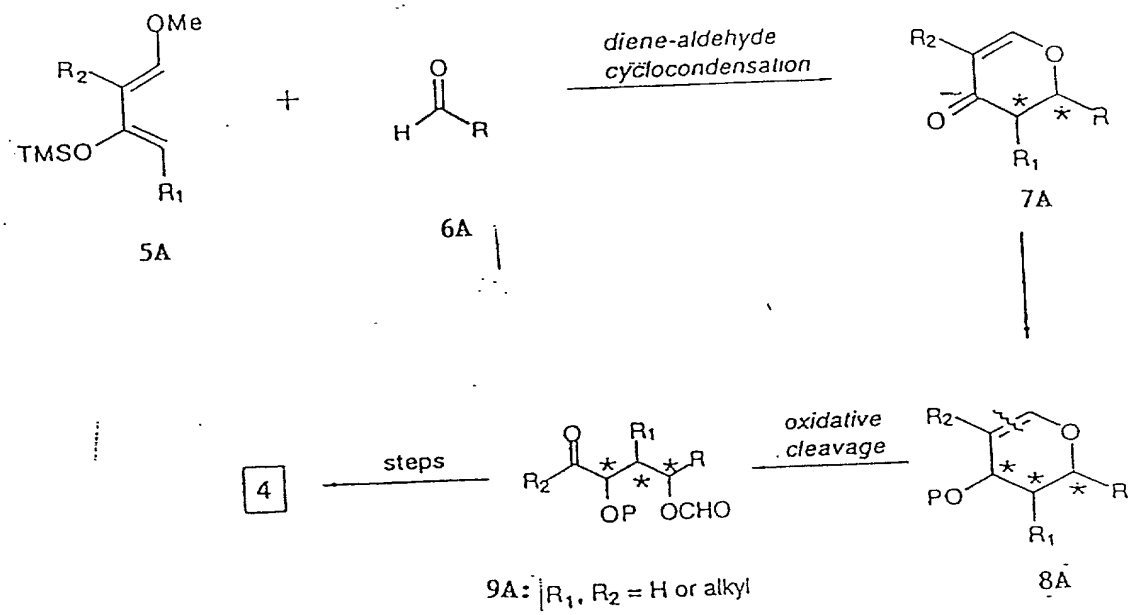

OMe
R2
TMSO
R1
5A
+
O
H
R
6A
diene-aldehyde
cyclocondensation
R2
O
O
R
R1
7A
4
steps
R1
R2
R
OP
OCHO
oxidative
cleavage
R2
O
PO
R
R1
8A
9A: R1, R2 = H or alkyl

Figure 13

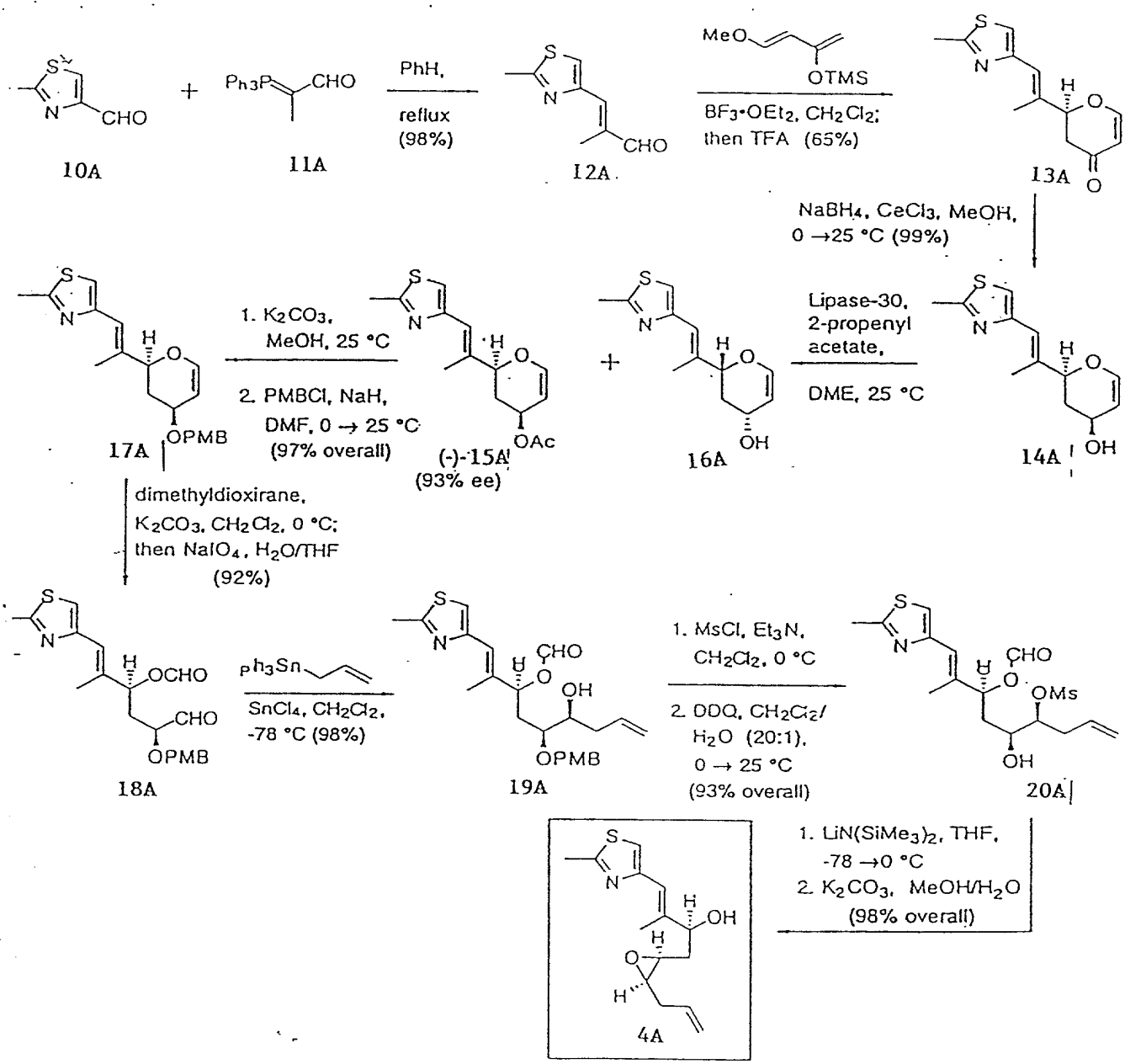

10A
11A
PhH, reflux (98%)
12A
MeO
OTMS
BF3•OEt2, CH2Cl2; then TFA (65%)
13A
NaBH4, CeCl3, MeOH, 0 →25 °C (99%)
1. K2CO3, MeOH, 25 °C
2. PMBCl, NaH, DMF, 0 → 25 °C (97% overall)
17A
(-)-15A (93% ee)
16A
Lipase-30, 2-propenyl acetate, DME, 25 °C
14A
dimethyldioxirane, K2CO3, CH2Cl2, 0 °C; then NaIO4, H2O/THF (92%)
18A
Ph3Sn
SnCl4, CH2Cl2, -78 °C (98%)
19A
1. MsCl, Et3N, CH2Cl2, 0 °C
2. DDQ, CH2Cl2/H2O (20:1), 0 → 25 °C (93% overall)
20A
1. LiN(SiMe3)2, THF, -78 →0 °C
2. K2CO3, MeOH/H2O (98% overall)
4A

Figure 14

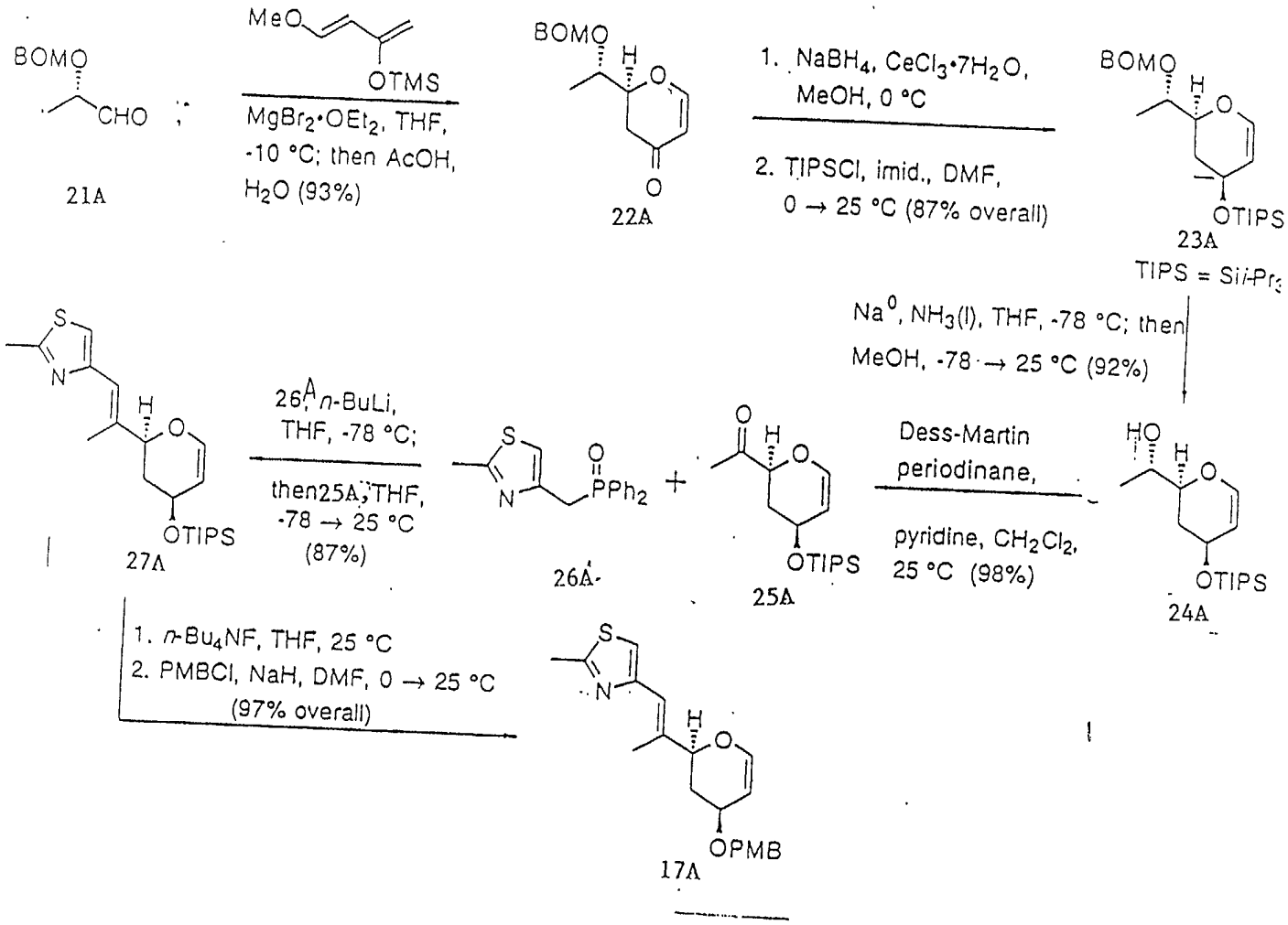
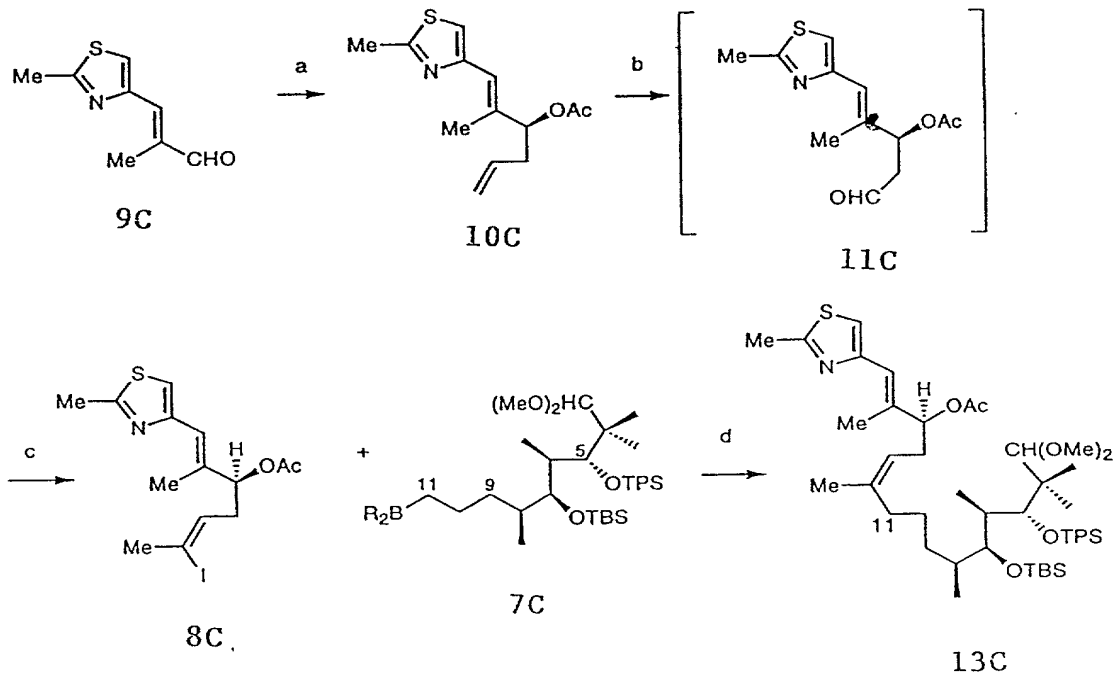

BOMO
CHO
21A
MeO
OTMS
MgBr2•OEt2, THF,
-10 °C; then AcOH,
H2O (93%)
BOMO
O
O
22A
1. NaBH4, CeCl3•7H2O,
MeOH, 0 °C
2. TIPSCl, imid., DMF,
0 → 25 °C (87% overall)
BOMO
OTIPS
23A
TIPS = SiiPr3
Na0, NH3(l), THF, -78 °C; then
MeOH, -78 → 25 °C (92%)
HO
OTIPS
24A
Dess-Martin
periodinane,
pyridine, CH2Cl2,
25 °C (98%)
O
OTIPS
25A
S
N
PPh2
26A
n-BuLi,
THF, -78 °C;
then 25A, THF,
-78 → 25 °C
(87%)
OTIPS
27A
1. n-Bu4NF, THF, 25 °C
2. PMBCl, NaH, DMF, 0 → 25 °C
(97% overall)
OPMB
17A

Figure 15


Me
S
N
Me
CHO
9C
a
Me
S
N
Me
OAc
10C
b
Me
S
N
Me
OAc
OHC
11C
c
Me
S
N
Me
H
OAc
Me
I
8C
+
(MeO)2HC
5
OTPS
11
9
R2B
OTBS
7C
d
Me
S
N
Me
H
OAc
Me
11
CH(OMe)2
OTPS
OTBS
13C

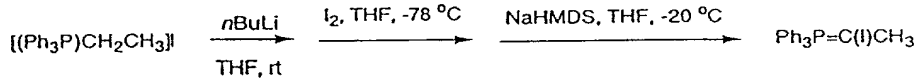

[(Ph3P)CH2CH3]I
nBuLi
THF, rt
I2, THF, -78 °C
NaHMDS, THF, -20 °C
Ph3P=C(I)CH3
12C

Figure 16

Patent Application Publication

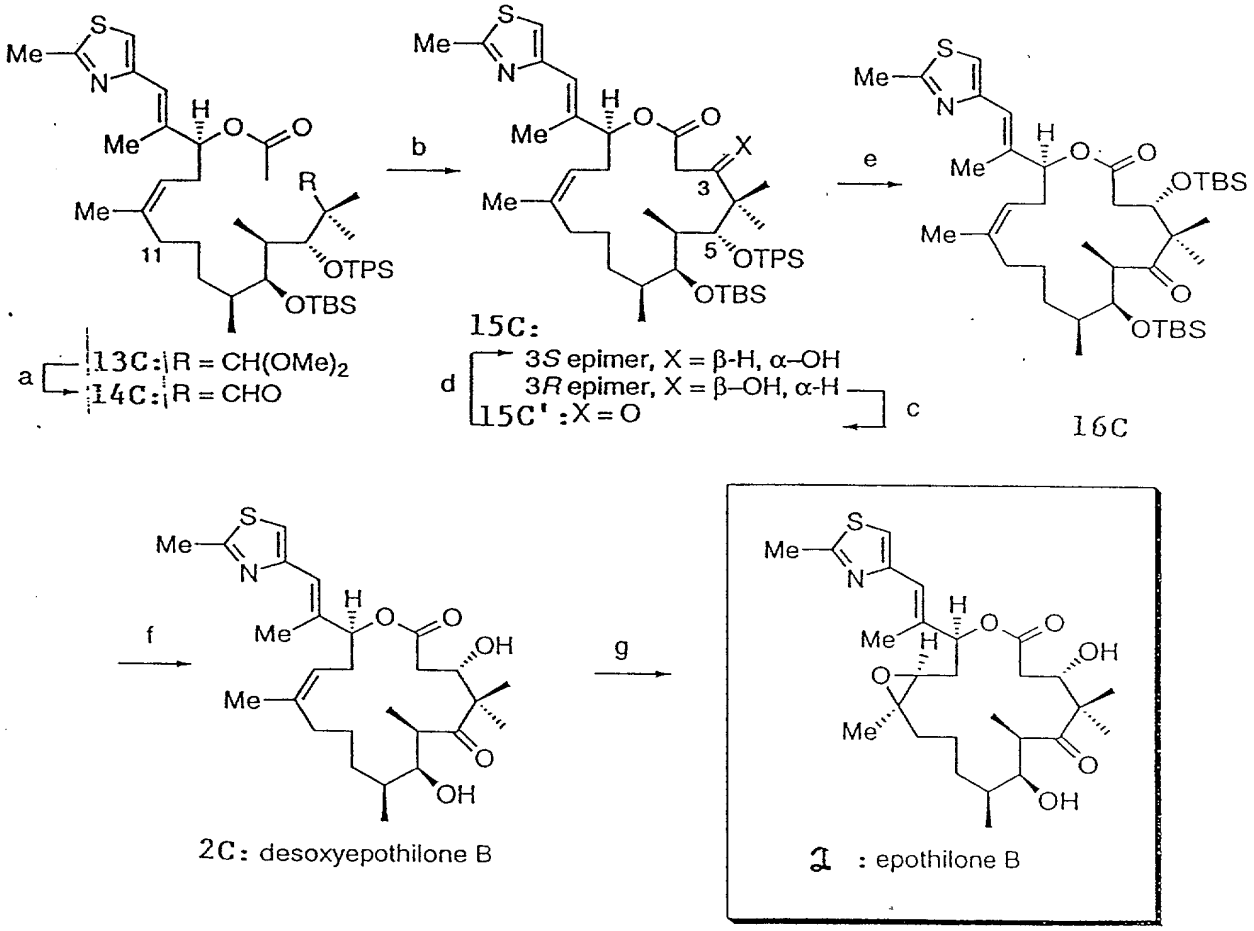


Figure 17

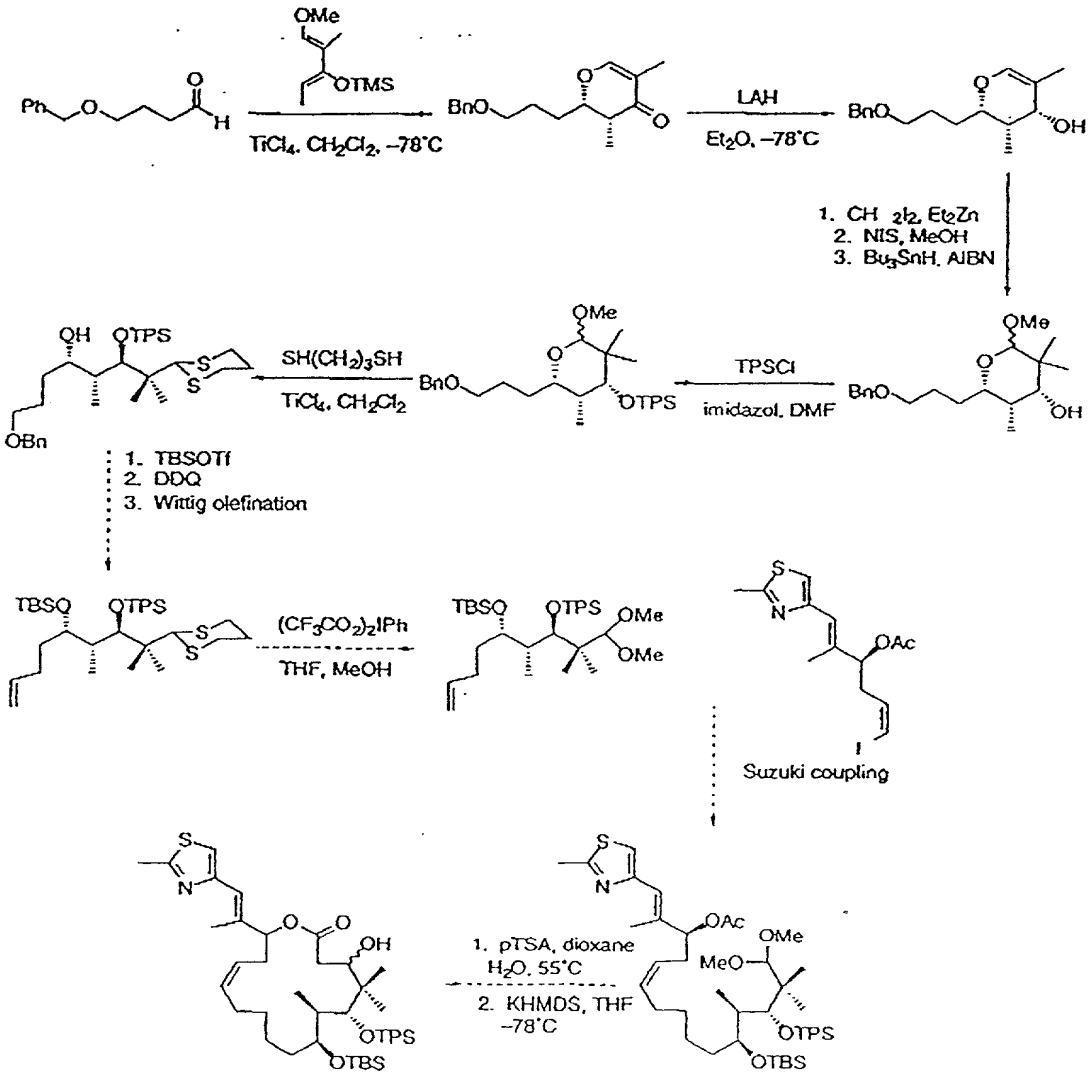

OMe
OTMS
TiCl4, CH2Cl2, –78°C
LAH
Et2O, –78°C
1. CH2I2, Et2Zn
2. NIS, MeOH
3. Bu3SnH, AIBN
TPSCl
imidazol, DMF
SH(CH2)3SH
TiCl4, CH2Cl2
1. TBSOTf
2. DDQ
3. Wittig olefination
(CF3CO2)2IPh
THF, MeOH
Suzuki coupling
1. pTSA, dioxane
H2O, 55°C
2. KHMDS, THF
–78°C

Figure 18

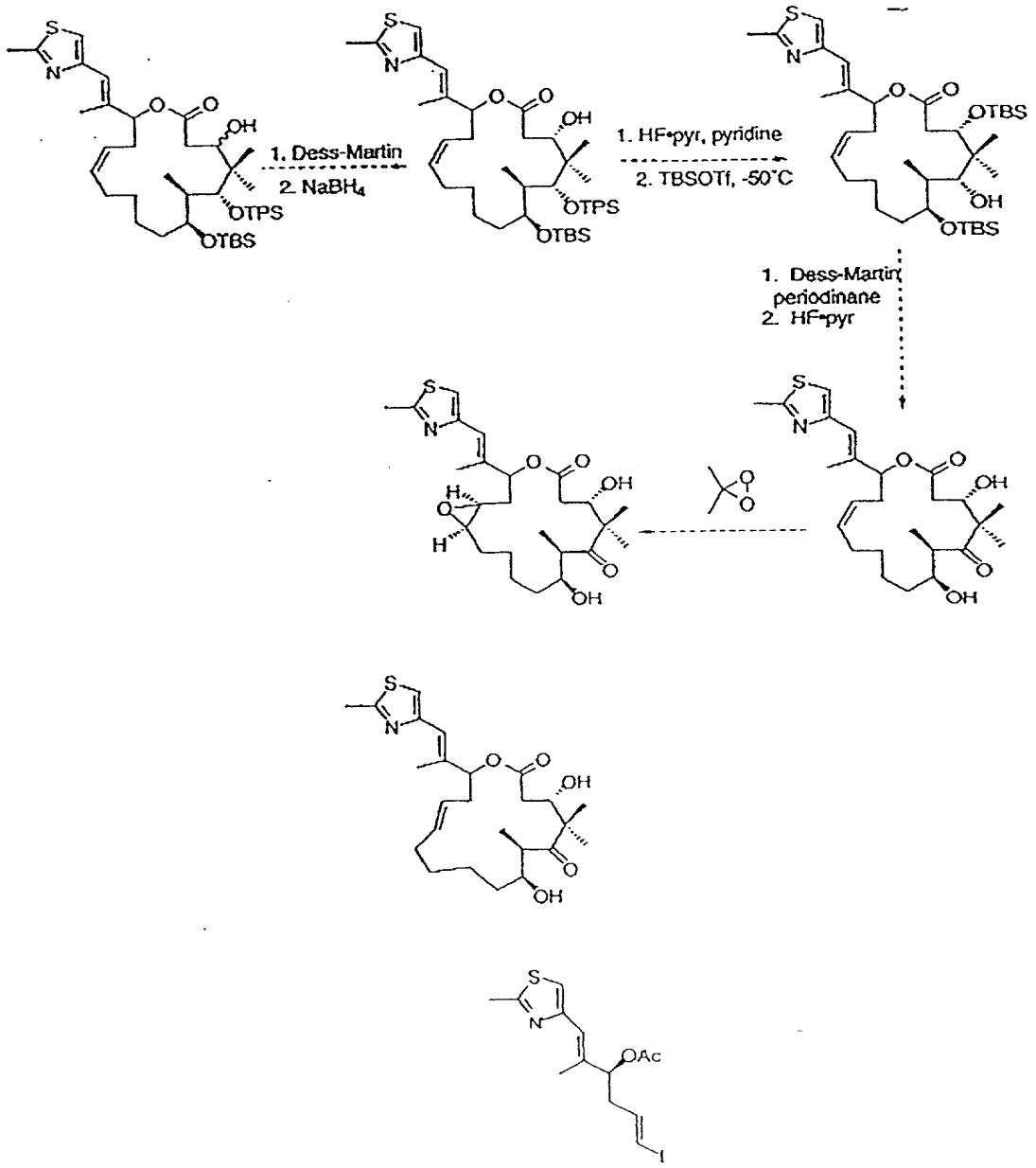
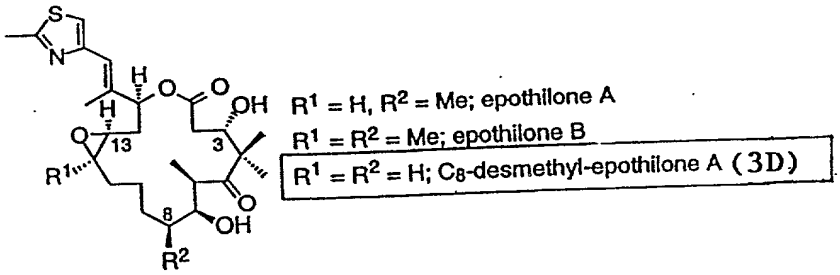

1. Dess-Martin
2. NaBH4
1. HF•pyr, pyridine
2. TBSOTf, -50°C
1. Dess-Martin periodinane
2. HF•pyr
OTPS
OTBS
OH
OAc

Figure 19


R1 = H, R2 = Me; epothilone A
R1 = R2 = Me; epothilone B
R1 = R2 = H; C8-desmethyl-epothilone A (3D)

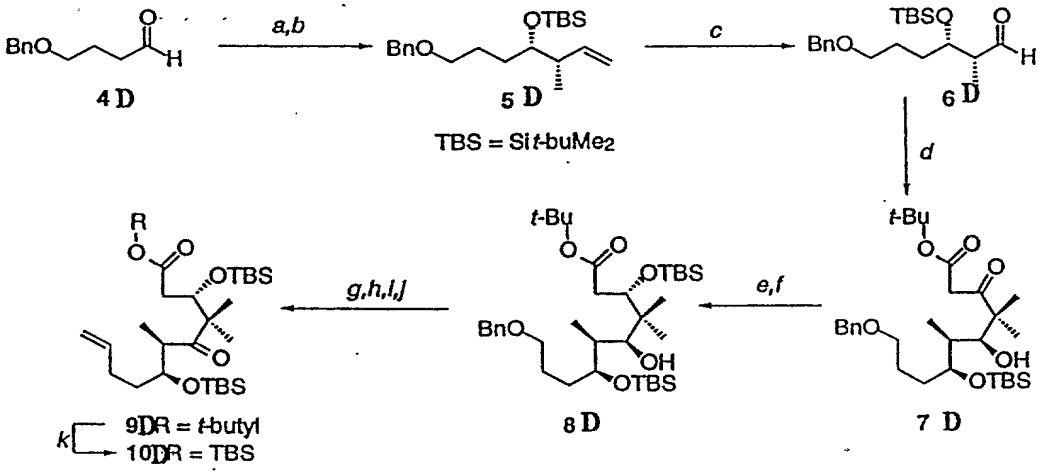

4 D
a,b
5 D
TBS = Si t-buMe2
c
6 D
d
7 D
e,f
8 D
g,h,I,j
9D R = t-butyl
k
10D R = TBS

FIGURE 20

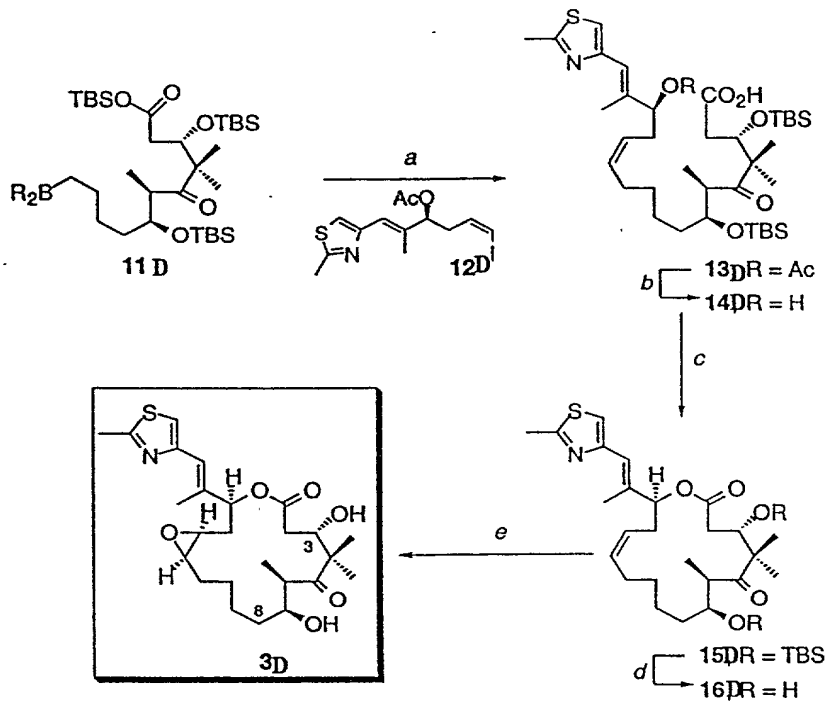

TBSO
OTBS
R2B
OTBS
11D
a
AcO
12D
OR
CO2H
OTBS
OTBS
13DR = Ac
b
14DR = H
c
OR
OR
15DR = TBS
d
16DR = H
e
OH
OH
3D

FIGURE 21

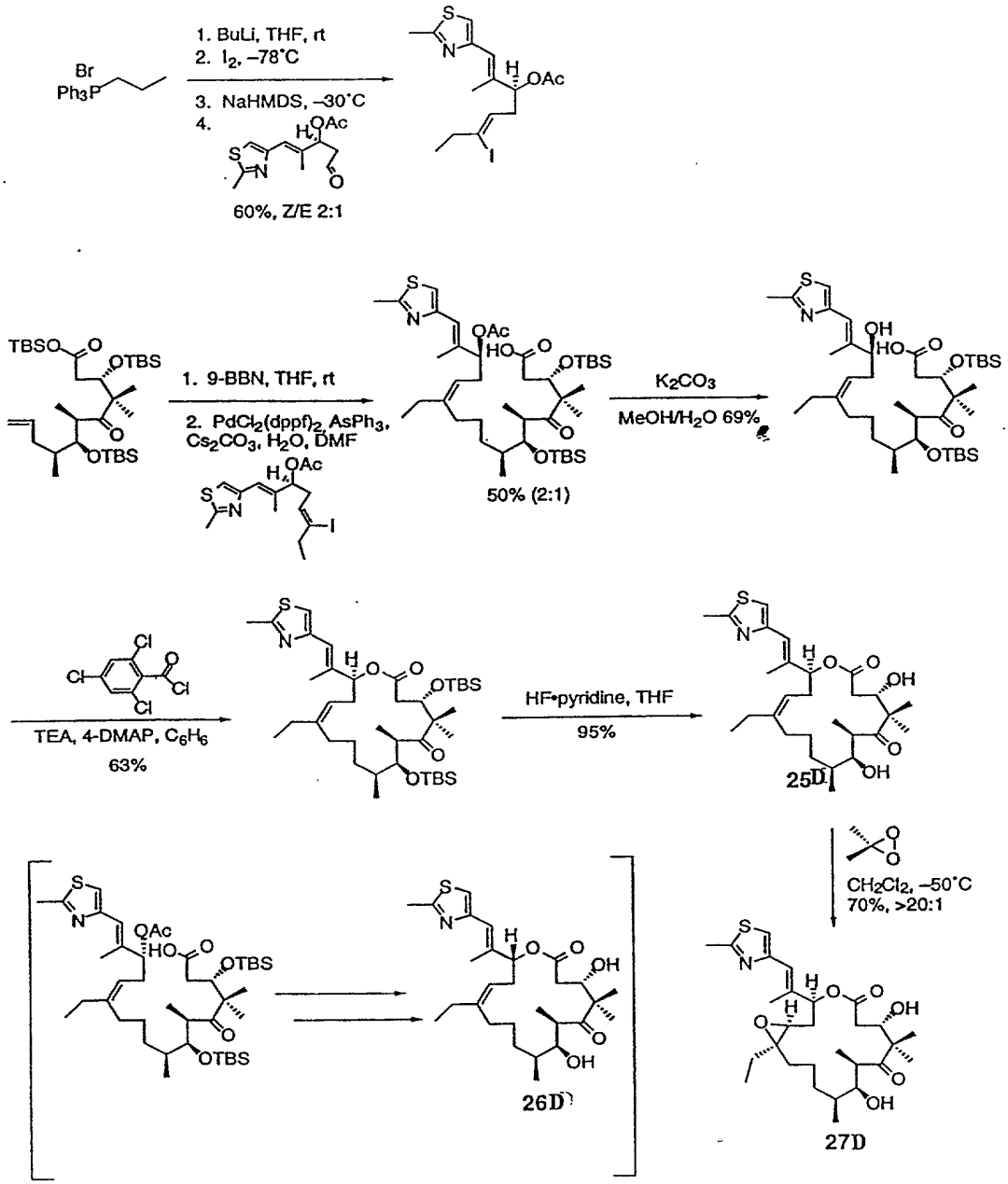

1. BuLi, THF, rt
2. I2, –78°C
3. NaHMDS, –30°C
4.
60%, Z/E 2:1
1. 9-BBN, THF, rt
2. PdCl2(dppf)2, AsPh3, Cs2CO3, H2O, DMF
50% (2:1)
K2CO3
MeOH/H2O 69%
TEA, 4-DMAP, C6H6
63%
HF•pyridine, THF
95%
25D
CH2Cl2, –50°C
70%, >20:1
26D
27D

FIGURE 22

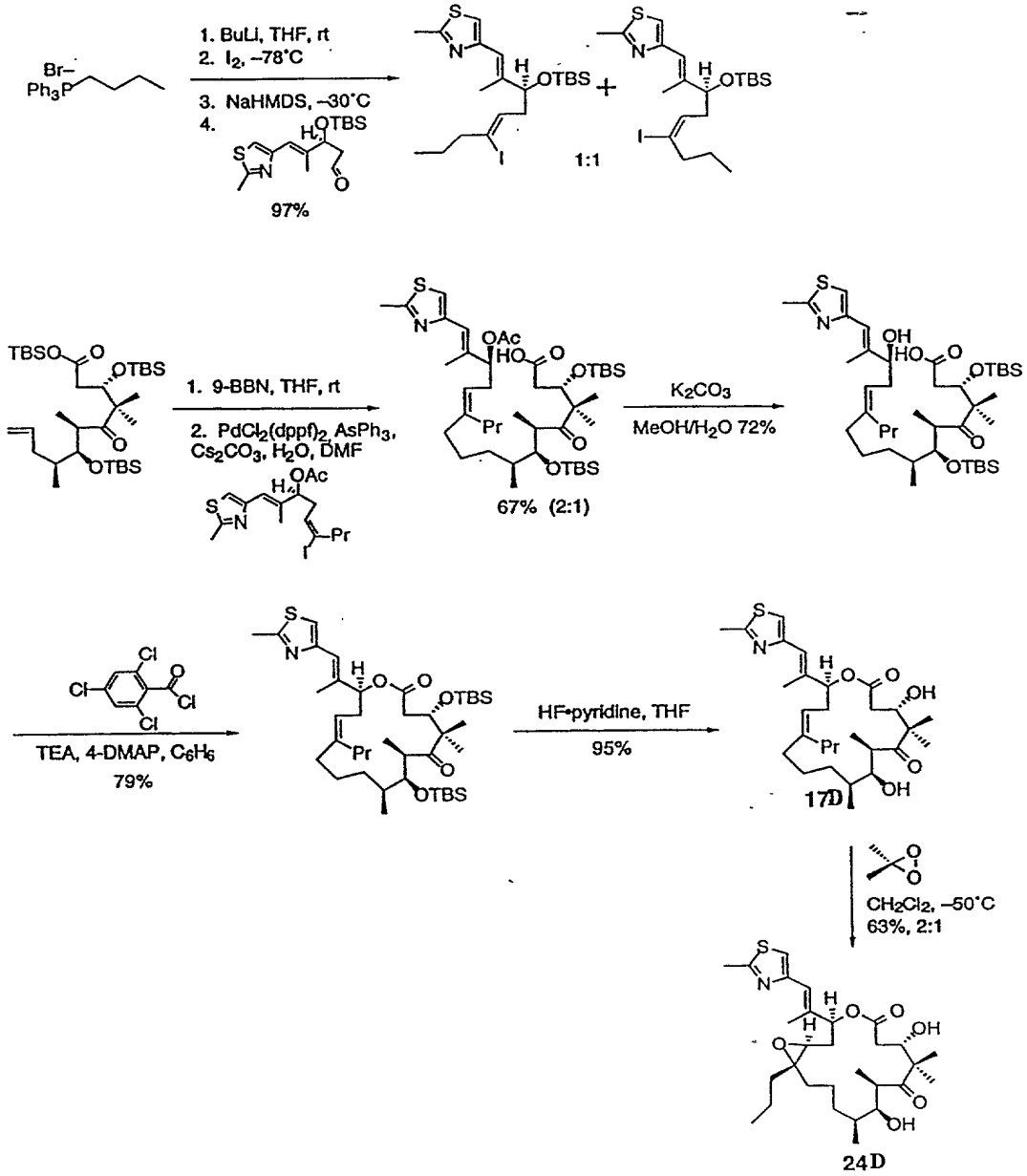

1. BuLi, THF, rt
2. I2, –78°C
3. NaHMDS, –30°C
4.
97%
1:1
1. 9-BBN, THF, rt
2. PdCl2(dppf)2, AsPh3, Cs2CO3, H2O, DMF
67% (2:1)
K2CO3
MeOH/H2O 72%
TEA, 4-DMAP, C6H6
79%
HF•pyridine, THF
95%
17D
CH2Cl2, –50°C
63%, 2:1
24D

FIGURE 23

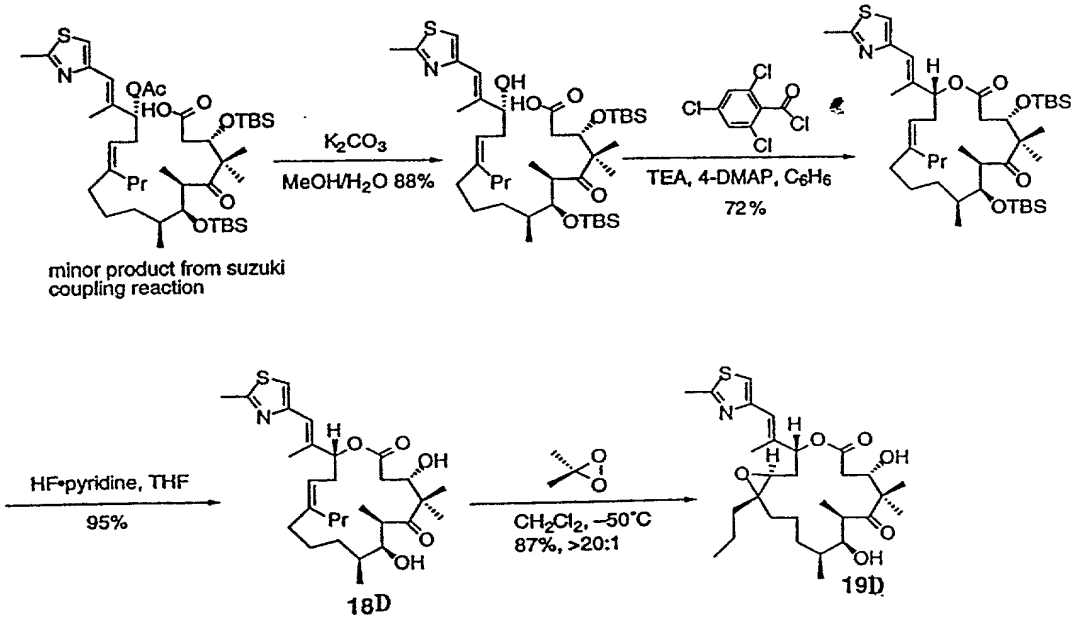

OAc
HO
OTBS
Pr
O
OTBS
minor product from suzuki coupling reaction
K_2CO_3
MeOH/H_2O 88%
OH
HO
OTBS
Pr
O
OTBS
Cl
Cl
Cl
O
Cl
TEA, 4-DMAP, C_6H_6
72%
H
O
O
OTBS
Pr
O
OTBS
HF•pyridine, THF
95%
H
O
O
OH
Pr
O
OH
18D
CH_2Cl_2, –50°C
87%, >20:1
H
H
O
O
OH
O
OH
19D

FIGURE 24

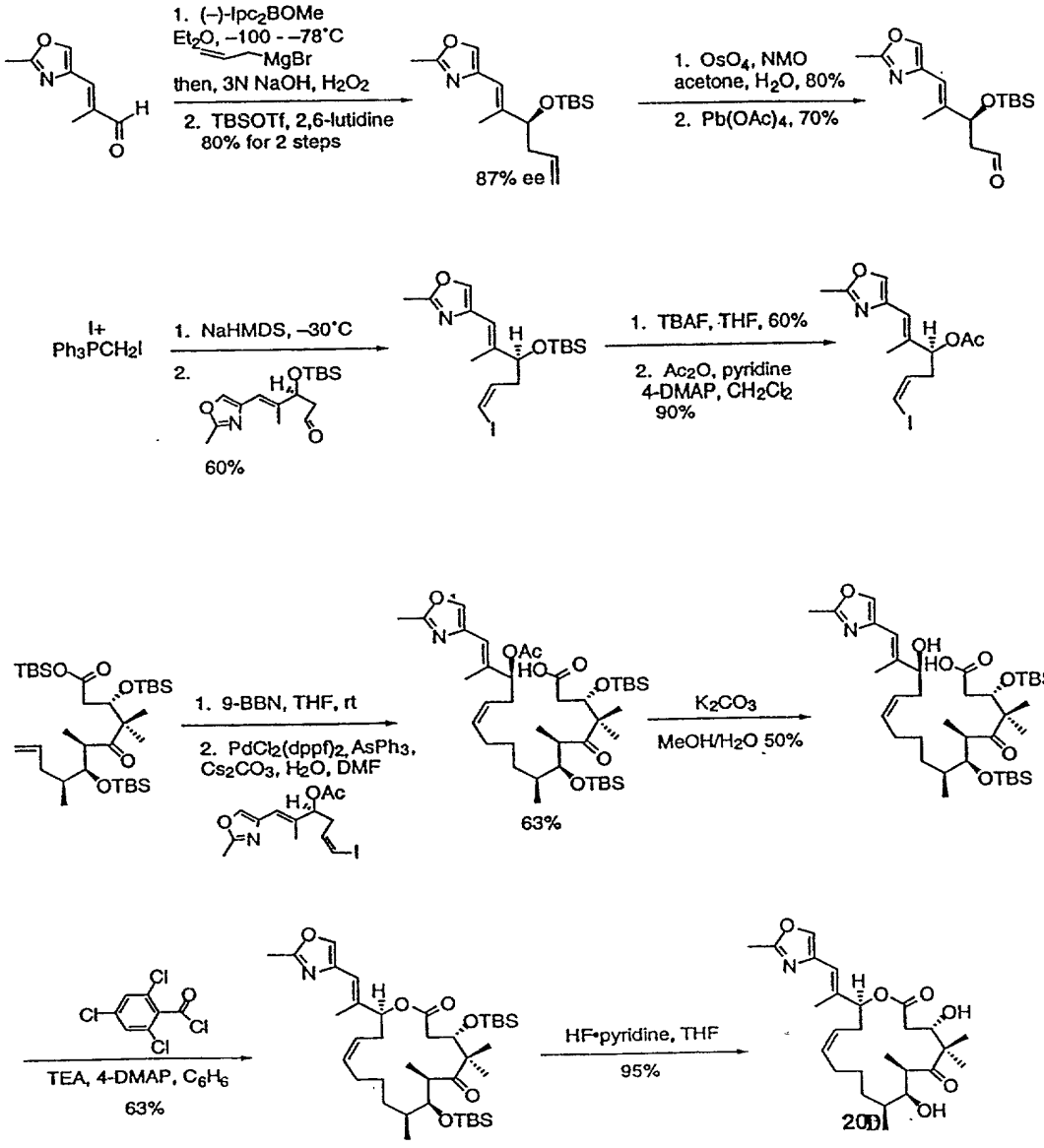

1. (–)-Ipc2BOMe
Et2O, –100 - –78°C
MgBr
then, 3N NaOH, H2O2
2. TBSOTf, 2,6-lutidine
80% for 2 steps
87% ee
1. OsO4, NMO
acetone, H2O, 80%
2. Pb(OAc)4, 70%
I+
Ph3PCH2I
1. NaHMDS, –30°C
2.
60%
1. TBAF, THF, 60%
2. Ac2O, pyridine
4-DMAP, CH2Cl2
90%
1. 9-BBN, THF, rt
2. PdCl2(dppf)2, AsPh3,
Cs2CO3, H2O, DMF
63%
K2CO3
MeOH/H2O 50%
TEA, 4-DMAP, C6H6
63%
HF•pyridine, THF
95%
20

FIGURE 25

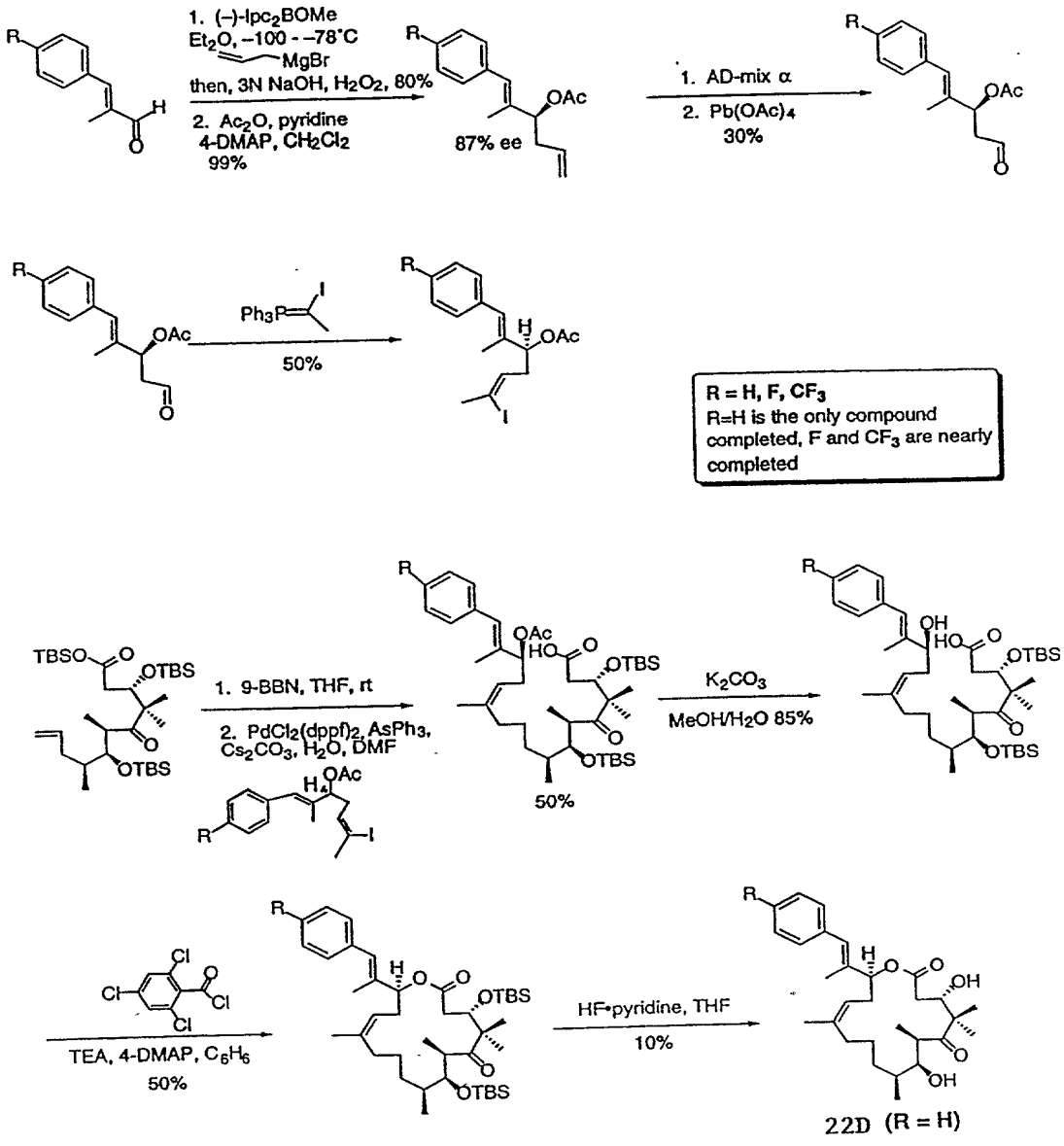

1. (–)-Ipc2BOMe
Et2O, –100 - –78°C
MgBr
then, 3N NaOH, H2O2, 80%
2. Ac2O, pyridine
4-DMAP, CH2Cl2
99%
87% ee
1. AD-mix α
2. Pb(OAc)4
30%
Ph3P=
50%
R = H, F, CF3
R=H is the only compound completed, F and CF3 are nearly completed
1. 9-BBN, THF, rt
2. PdCl2(dppf)2, AsPh3, Cs2CO3, H2O, DMF
50%
K2CO3
MeOH/H2O 85%
TEA, 4-DMAP, C6H6
50%
HF•pyridine, THF
10%
22D (R = H)

FIGURE 26

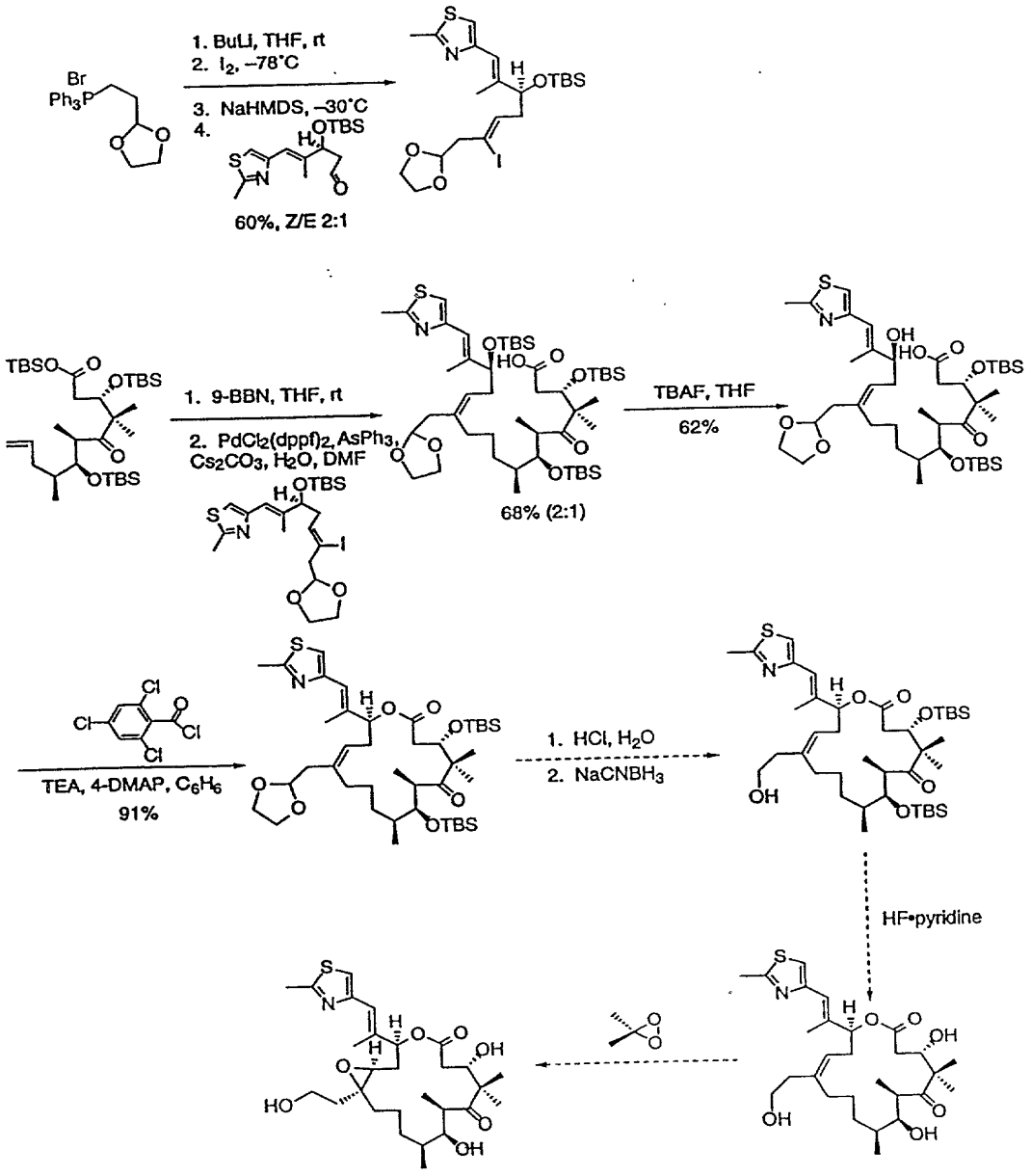
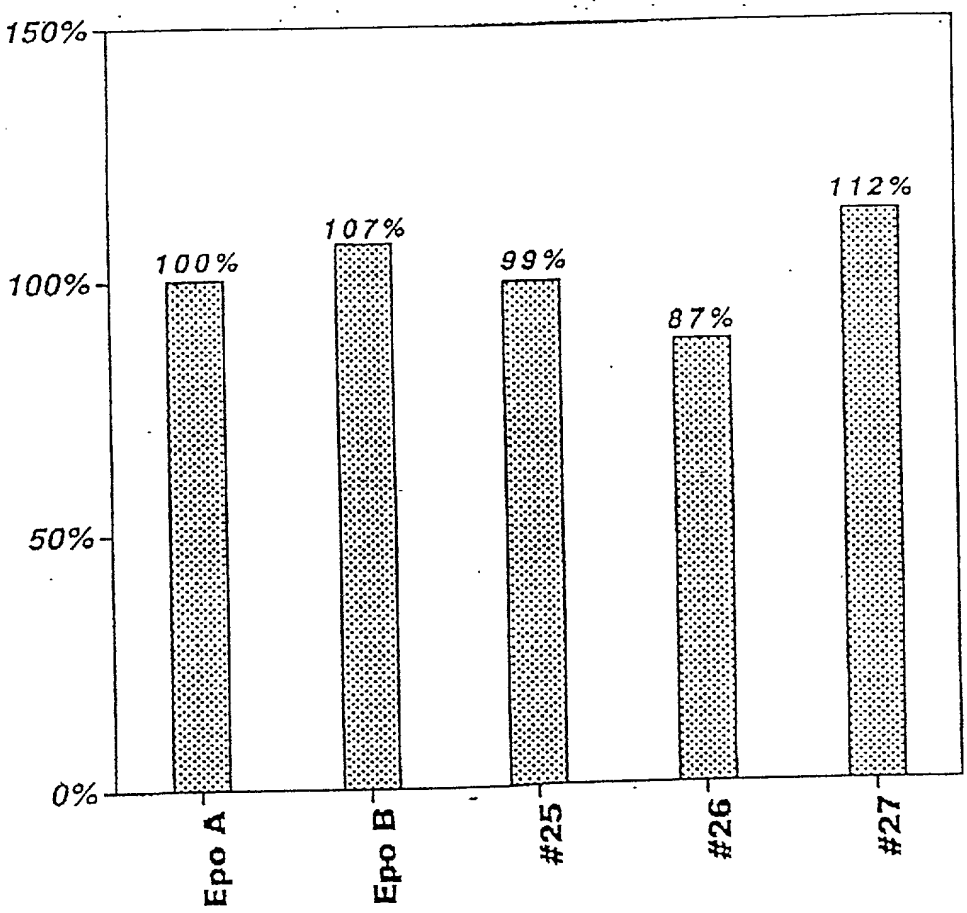

1. BuLi, THF, rt
2. I2, –78°C
3. NaHMDS, –30°C
4.
60%, Z/E 2:1
1. 9-BBN, THF, rt
2. PdCl2(dppf)2, AsPh3, Cs2CO3, H2O, DMF
68% (2:1)
TBAF, THF
62%
TEA, 4-DMAP, C6H6
91%
1. HCl, H2O
2. NaCNBH3
HF•pyridine

FIGURE 27


150%
100%
50%
0%
100%
107%
99%
87%
112%
Epo A
Epo B
#25
#26
#27

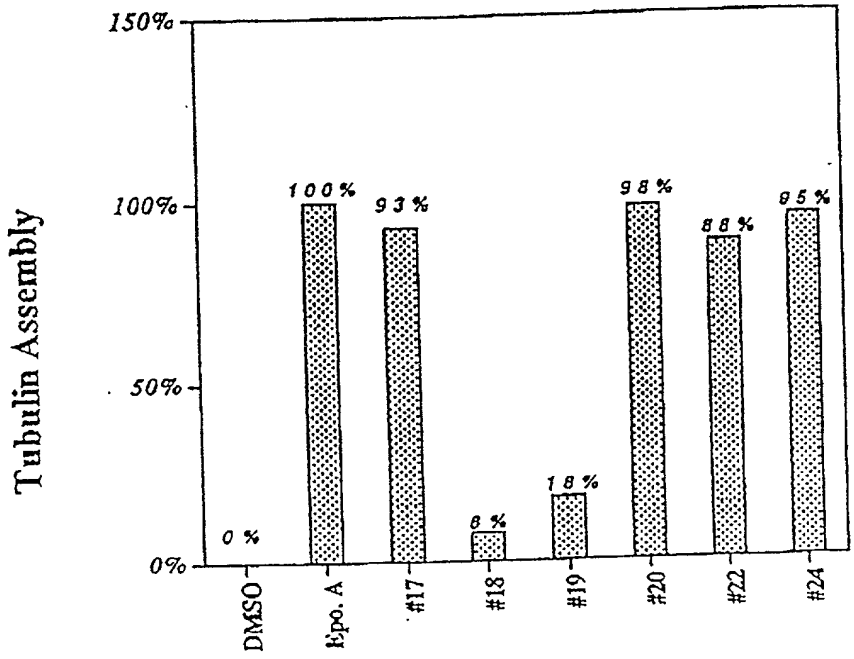

Tubulin Assembly
150%
100%
50%
0%
0 %
100%
93%
6%
18%
98%
88%
95%
DMSO
Epo. A
#17
#18
#19
#20
#22
#24

FIGURE 28

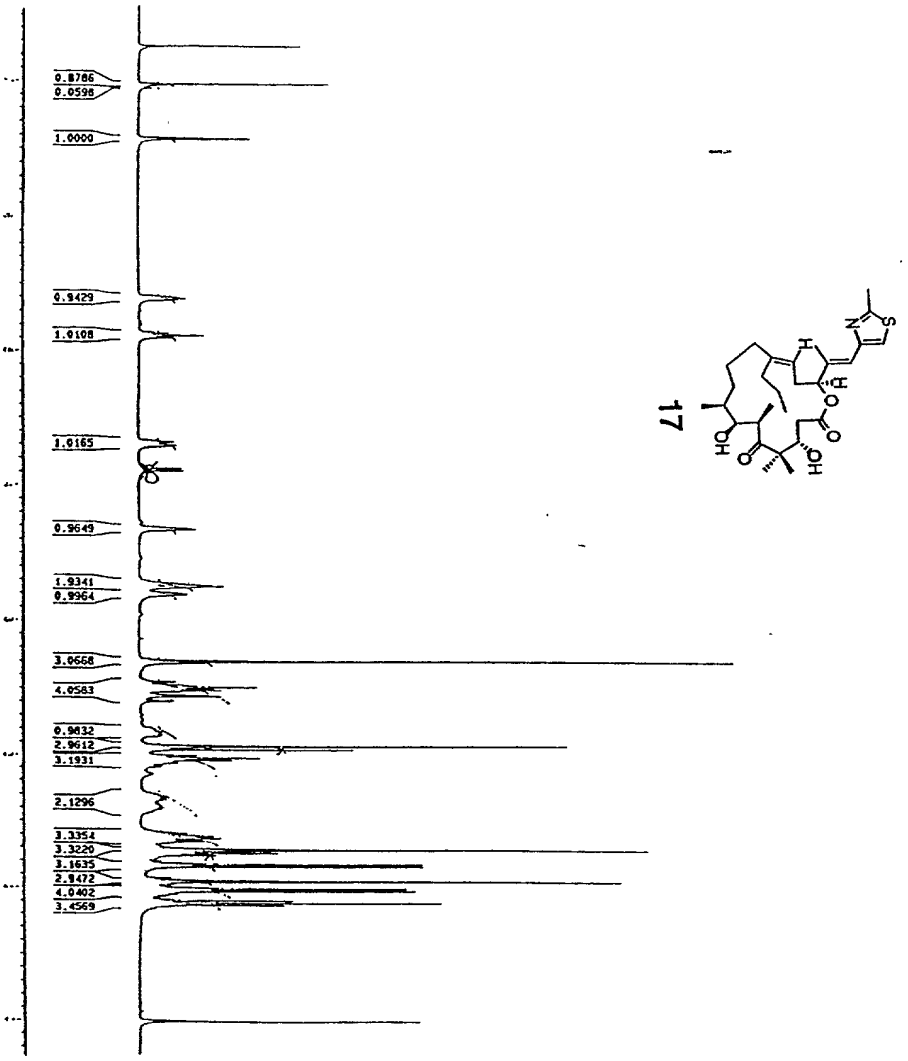

0.8786
0.0598
1.0000
0.9429
1.0108
1.0165
0.9649
1.9341
0.9964
3.0668
4.0583
0.9832
2.9612
3.1931
2.1296
3.3354
3.3220
3.1635
2.9472
4.0402
3.4569
17

FIGURE 29

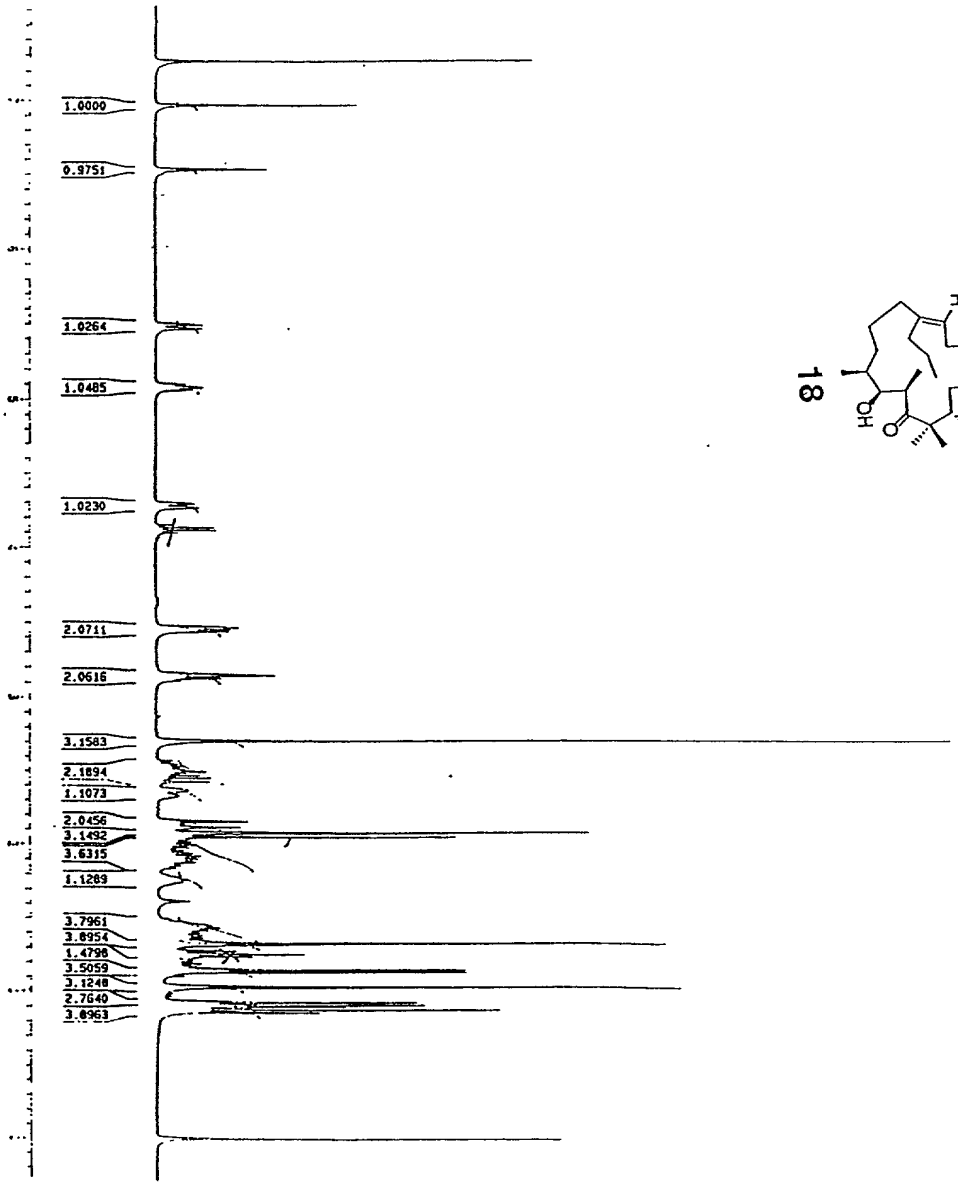
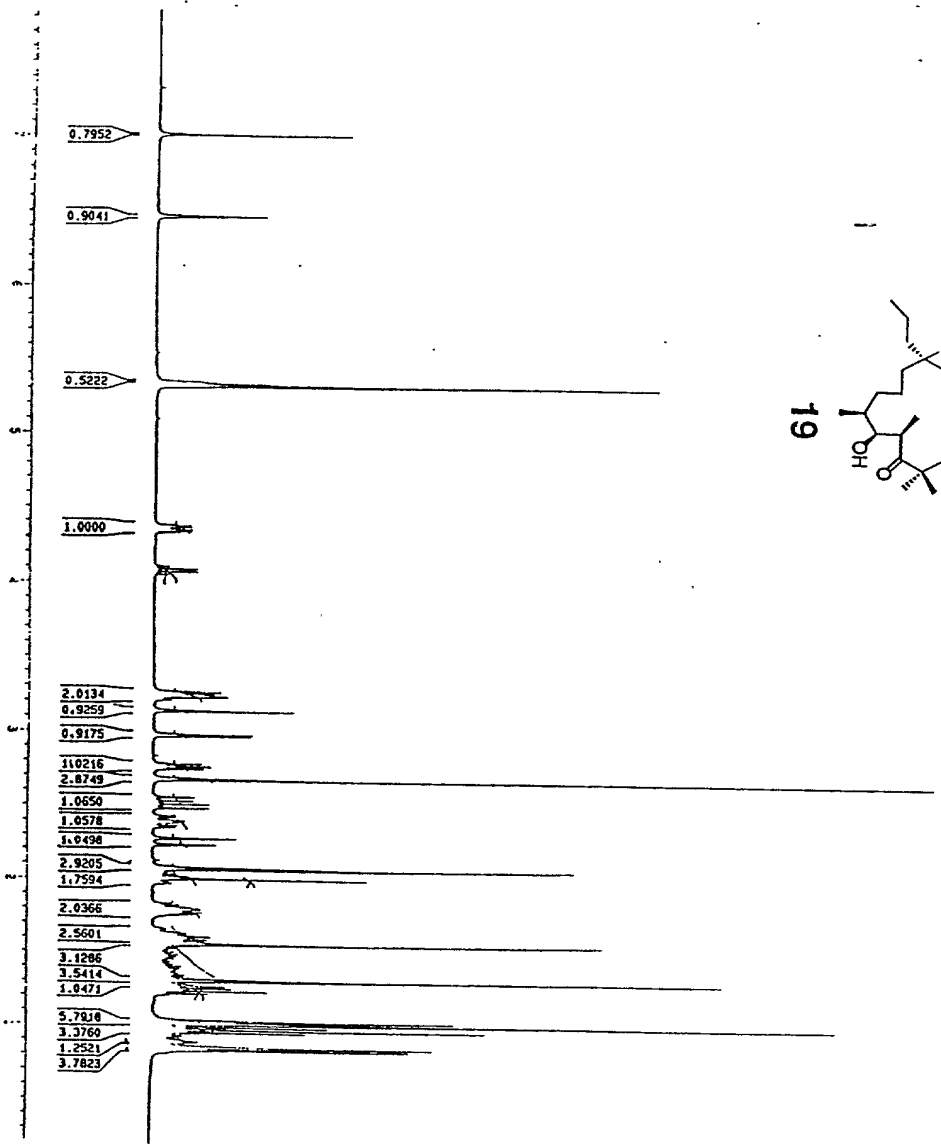
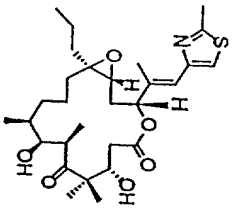

1.0000
0.9751
1.0264
1.0485
1.0230
2.0711
2.0616
3.1583
2.1894
1.1073
2.0456
3.1492
3.6315
1.1289
3.7961
3.8954
1.4798
3.5059
3.1248
2.7640
3.8963
18

FIGURE 30


0.7952
0.9041
0.5222
1.0000
2.0134
0.9259
0.9175
1.0216
2.8749
1.0650
1.0578
1.0498
2.9205
1.7594
2.0366
2.5601
3.1286
3.5414
1.0471
5.7910
3.3760
1.2521
3.7823



19

FIGURE 31

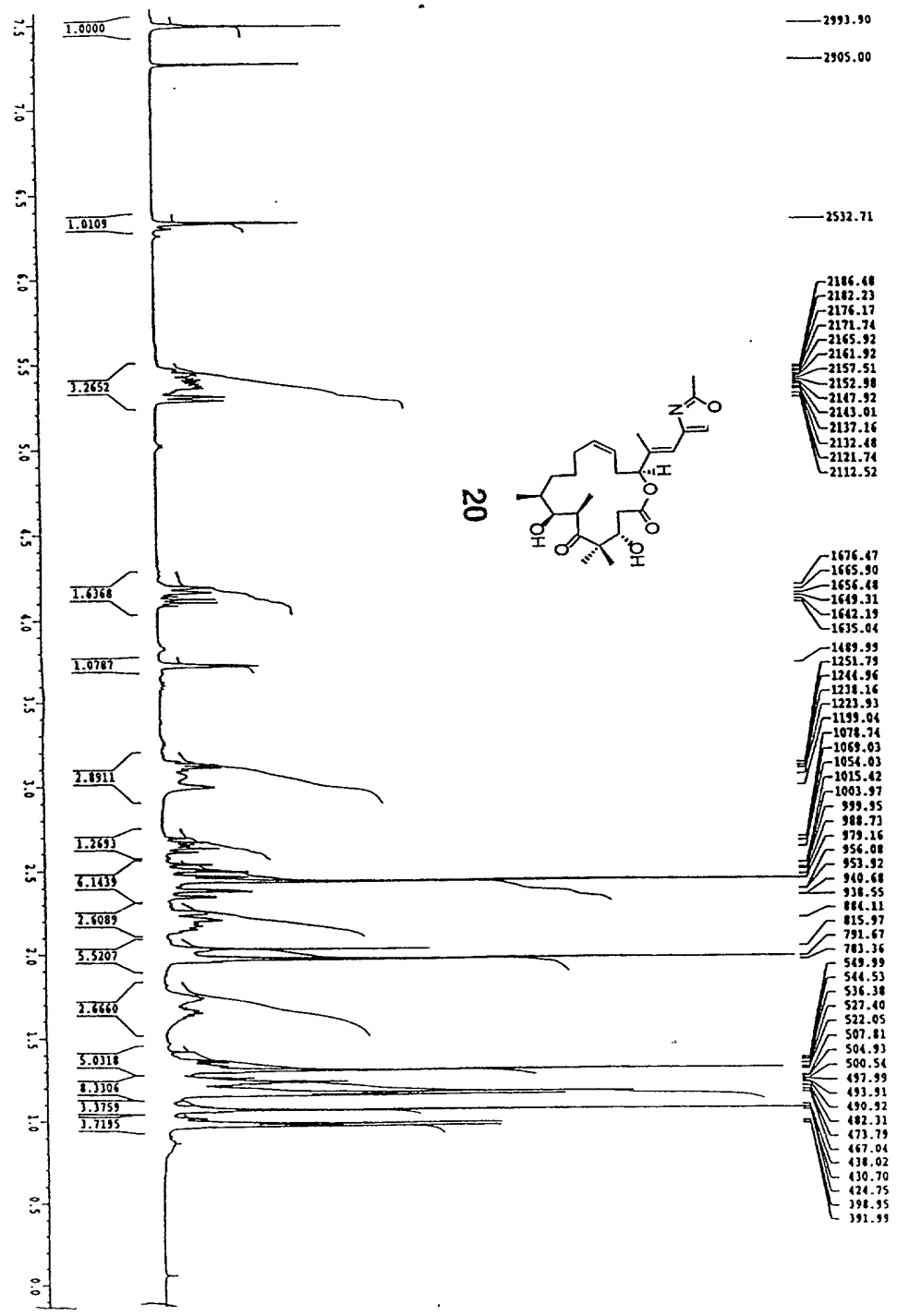

1.0000
1.0109
3.2652
1.6368
1.0787
2.8911
1.2693
4.1439
2.6089
5.5207
2.6660
5.0318
8.3306
3.3759
3.7195
2993.90
2905.00
2532.71
2186.48
2182.23
2176.17
2171.74
2165.92
2161.92
2157.51
2152.98
2147.92
2143.01
2137.16
2132.48
2121.74
2112.52
1676.47
1665.90
1656.48
1649.31
1642.19
1635.04
1489.99
1251.79
1244.96
1238.16
1223.93
1199.04
1078.74
1069.03
1054.03
1015.42
1003.97
999.95
988.73
979.16
956.08
953.92
940.68
938.55
884.11
815.97
791.67
783.36
549.99
544.53
536.38
527.40
522.05
507.81
504.93
500.54
497.99
493.91
490.92
482.31
473.79
467.04
438.02
430.70
424.75
398.95
391.99
20

FIGURE 32

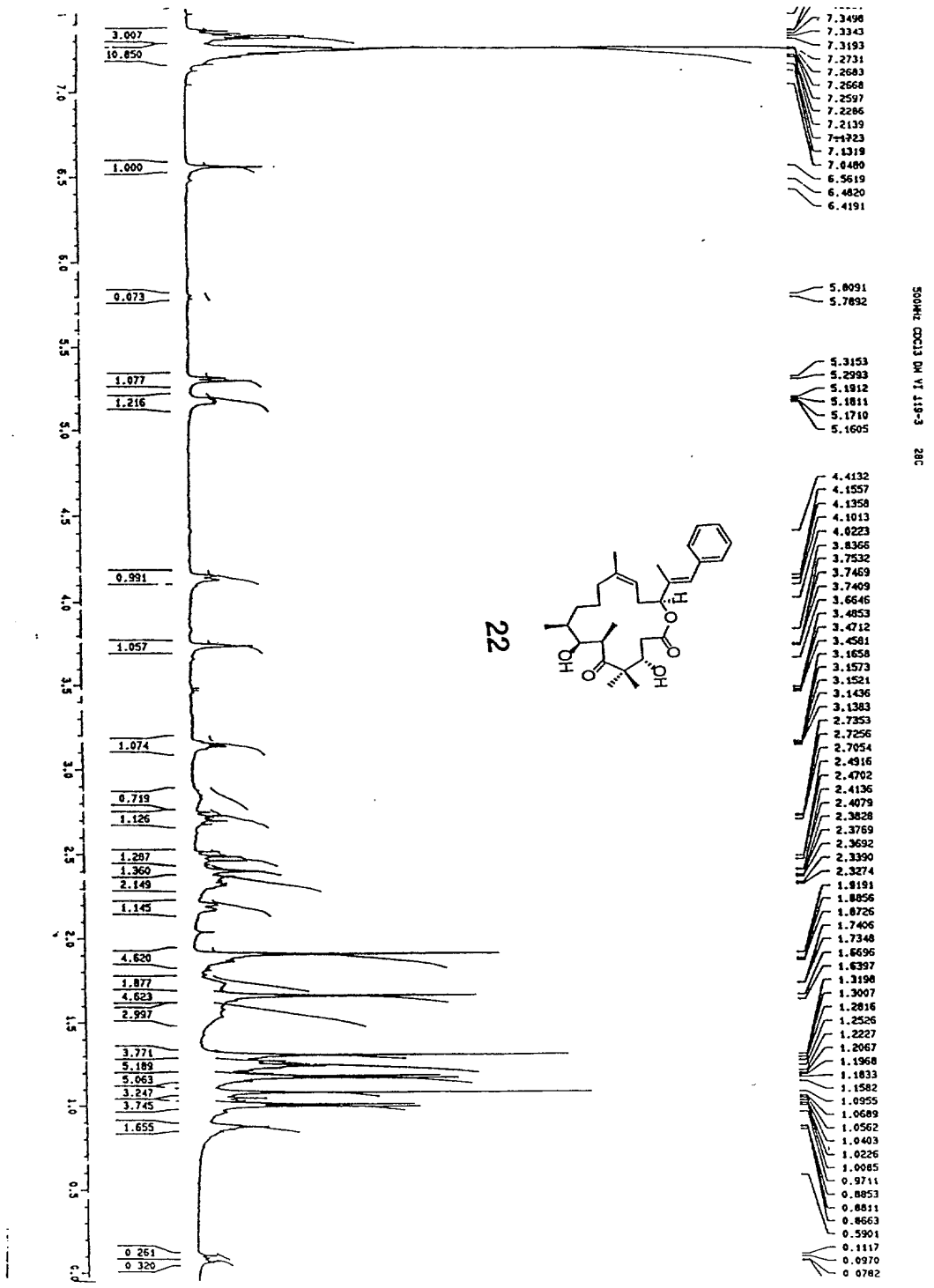


FIGURE 33

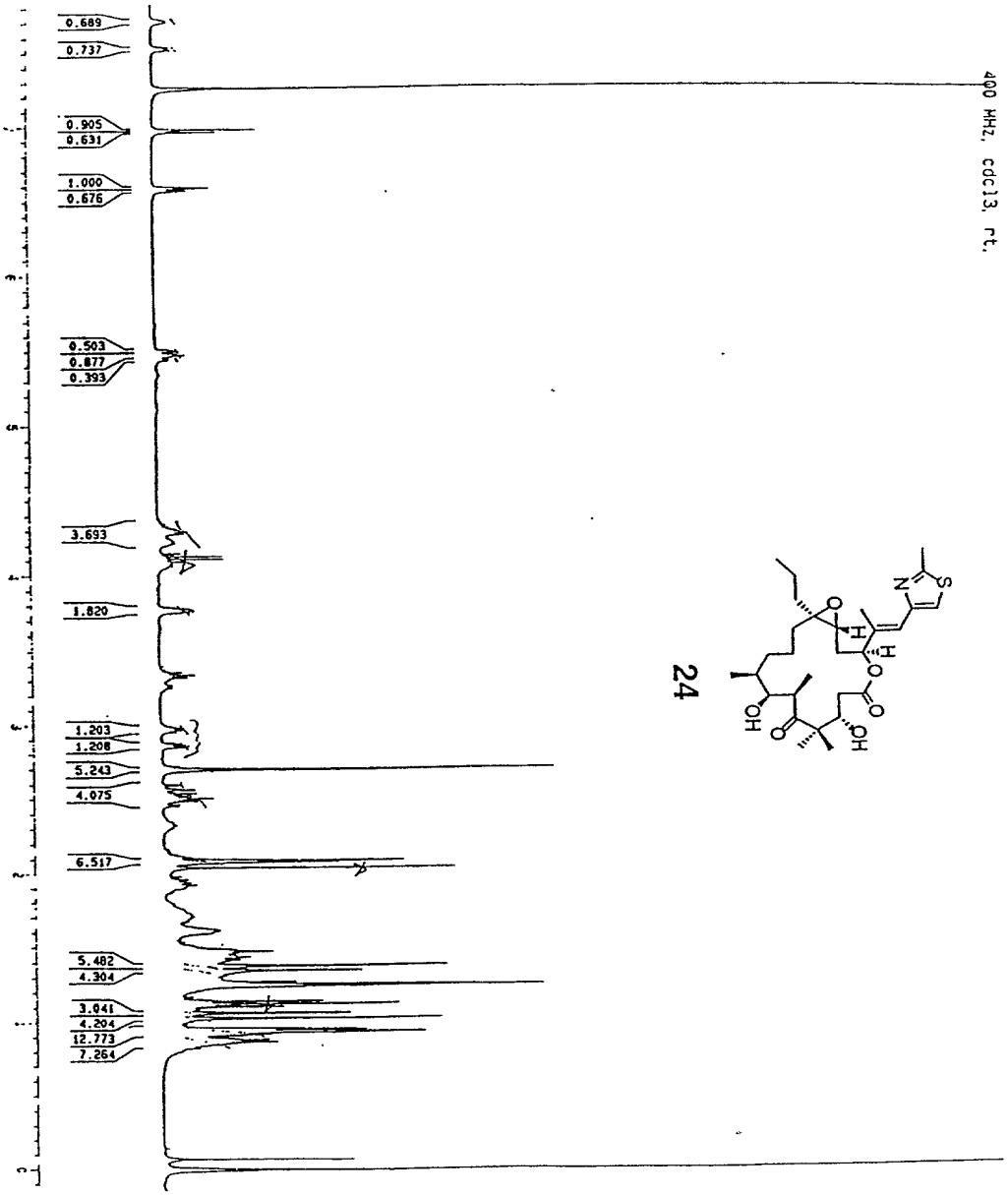

400 MHz, cdcl3, rt.
0.689
0.737
0.905
0.631
1.000
0.676
0.503
0.877
0.393
3.693
1.820
1.203
1.208
5.243
4.075
6.517
5.482
4.304
3.041
4.204
12.773
7.264
24

FIGURE 34

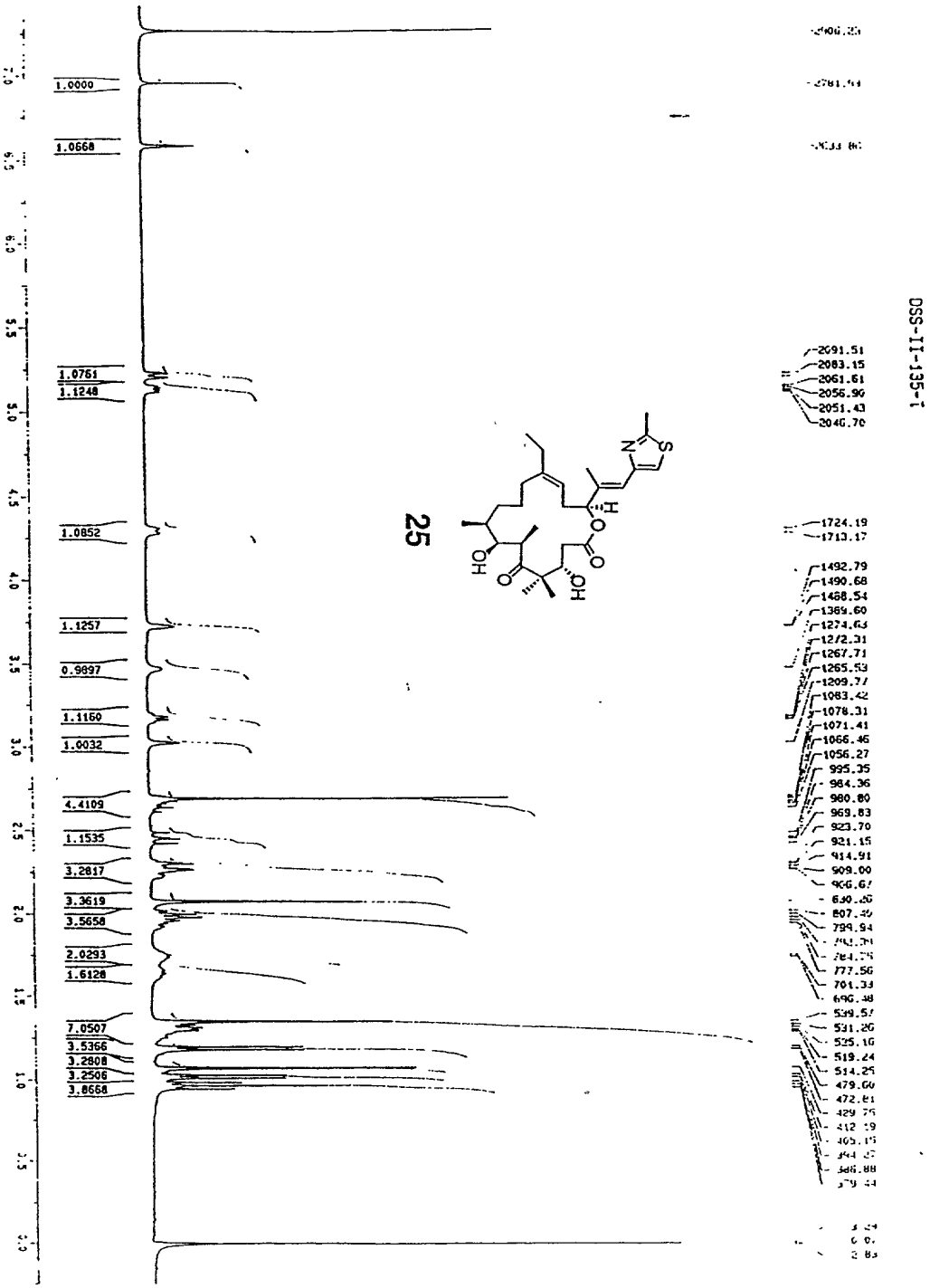

OSS-II-135-1
25
1.0000
1.0668
1.0761
1.1248
1.0852
1.1257
0.9897
1.1160
1.0032
4.4109
1.1535
3.2817
3.3619
3.5658
2.0293
1.6128
7.0507
3.5366
3.2808
3.2506
3.8668
2691.51
2083.15
2061.61
2056.90
2051.43
2046.70
1724.19
1713.17
1492.79
1490.68
1488.54
1389.60
1274.63
1272.31
1267.71
1265.53
1209.77
1083.42
1078.31
1071.41
1066.46
1056.27
995.35
984.36
980.80
969.83
923.70
921.15
914.91
909.00
807.49
799.94
777.56
701.33
539.57
531.26
525.10
519.24
514.25
479.60
472.81

FIGURE 35

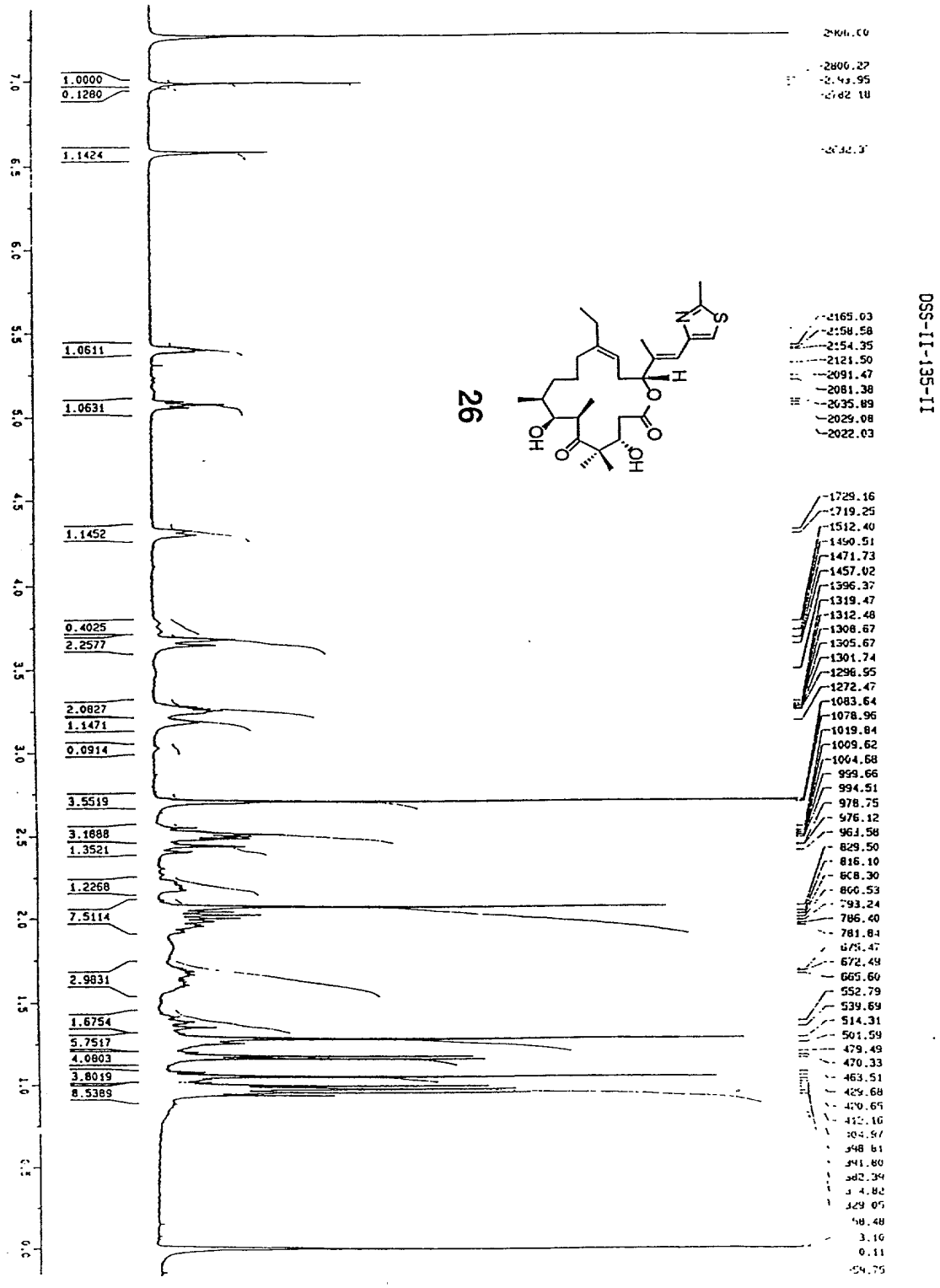

DSS-II-135-II
26
1.0000
0.1280
1.1424
1.0611
1.0631
1.1452
0.4025
2.2577
2.0827
1.1471
0.0914
3.5519
3.1688
1.3521
1.2268
7.5114
2.9831
1.6754
5.7517
4.0803
3.8019
8.5389

FIGURE 36

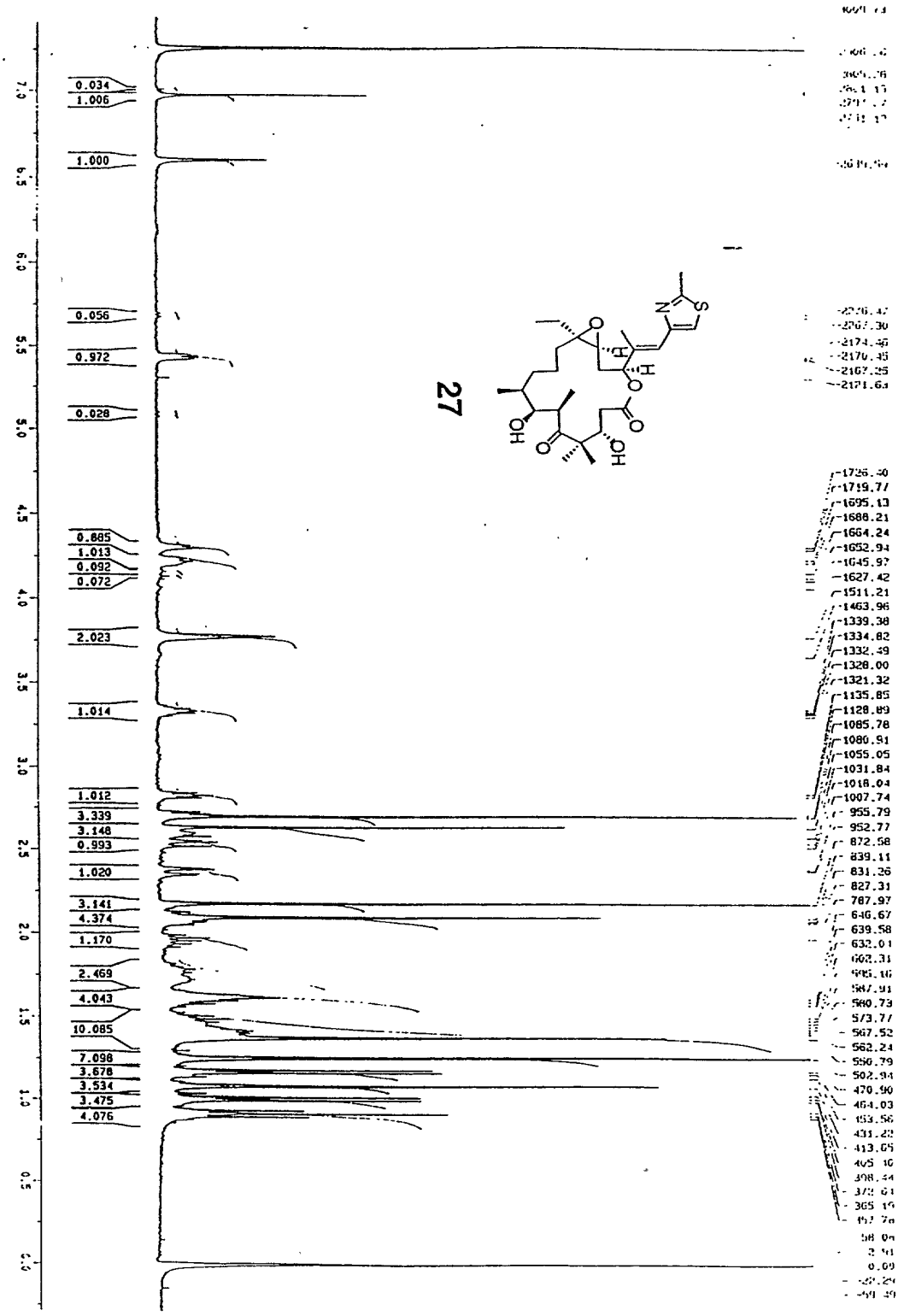

27
OSS-II-138-II
0.034
1.006
1.000
0.056
0.972
0.028
0.885
1.013
0.092
0.072
2.023
1.014
1.012
3.339
3.148
0.993
1.020
3.141
4.374
1.170
2.469
4.043
10.085
7.098
3.678
3.534
3.475
4.076

FIGURE 37

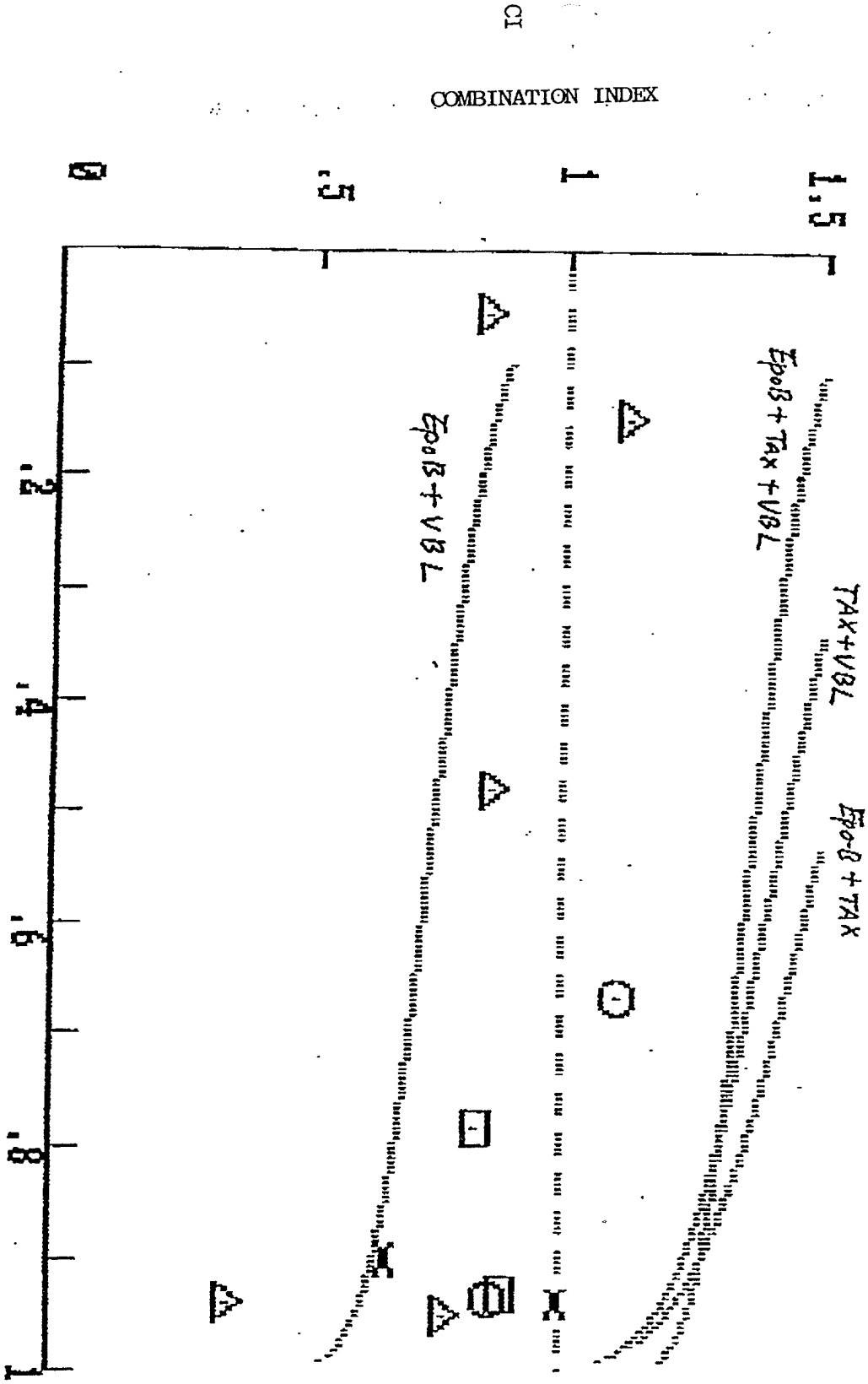
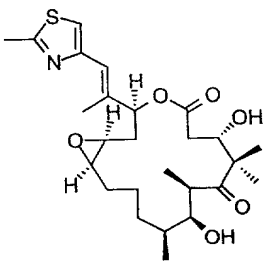
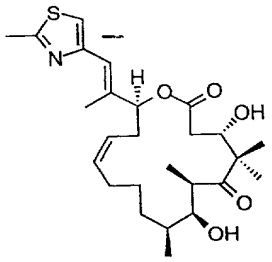

CI
COMBINATION INDEX
1.5
1
.5
0
.2
.4
.6
.8
1
FRACTIONAL EFFECT (Fa)
TAX+VBL
Epo-B + TAX
Epo B + Tax + VBL
Epo B + VBL

Figure 38

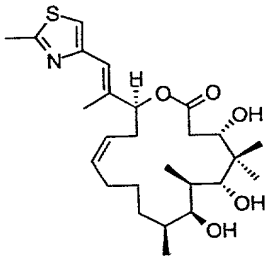


epothilone A
(0.0027)
[0.020]

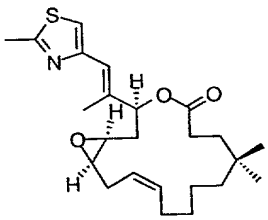


desoxyepothilone A

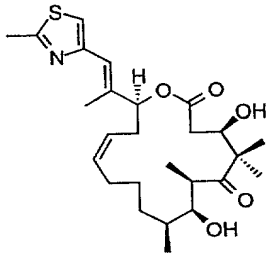
1
(0.022)
[0.012]



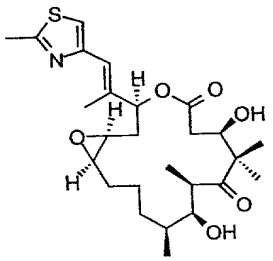
2
(14.23)
[6.28]



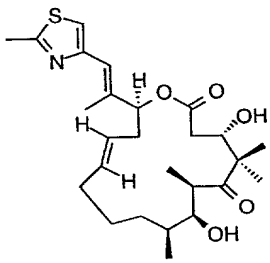
3
(271.1)
[22.4]



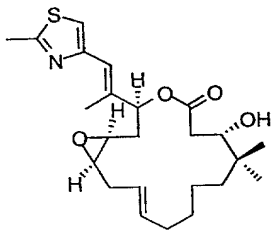
4
(2.12)
[43.0]



5
(>20)
[35.2]

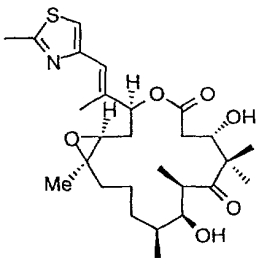


6
(0.052)
[0.035]



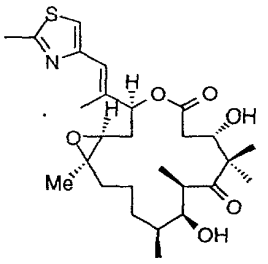
7
(7.36)
[9.82]

Fig. 39



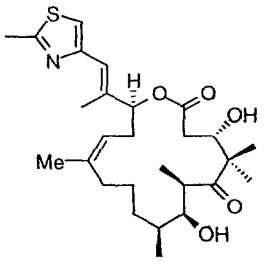
synthetic epothilone B

8
(0.00044)
[0.0026]



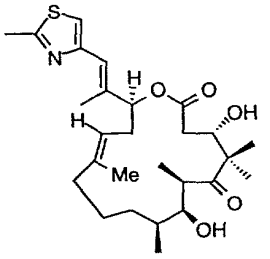
natural epothilone B

9
(0.00017)
[0.0012]

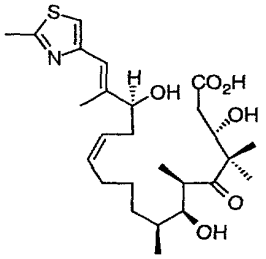


desoxyepothilone B

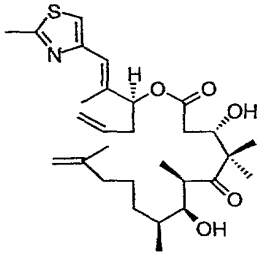
10
(0.0095)
[0.017]



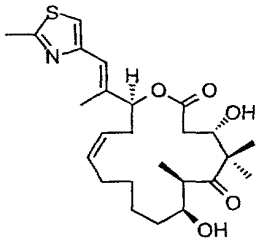
11
(0.090)
[0.262]



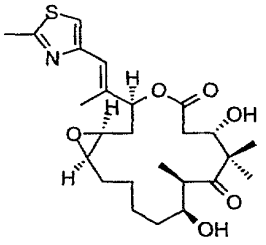
12
(0.79)
[>5]



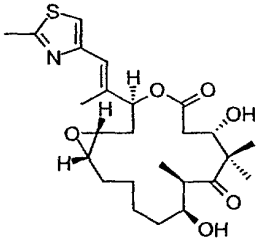
13
(11.53)
[5.63]



14
(5.42)
[5.75]

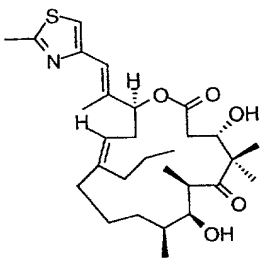


15
(0.96)
[5.95]

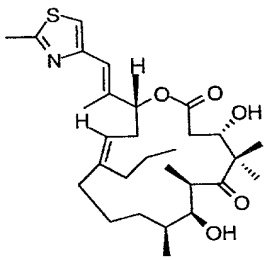


16
(7.47)
[16.48]

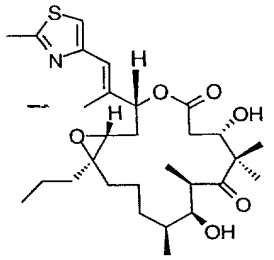
Fig. 40



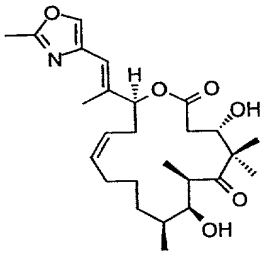
17
(0.090)
[0.254]



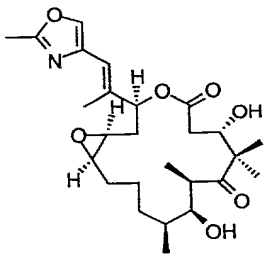
18
(1158)
[>720]



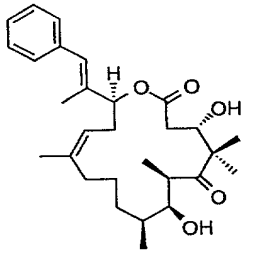
19
(0.96)
[>1.0]



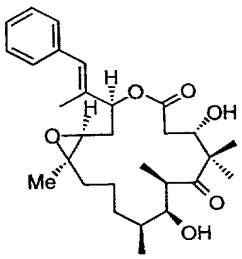
20
(0.030)
[0.049]



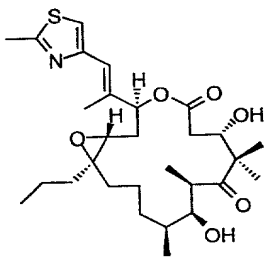
21



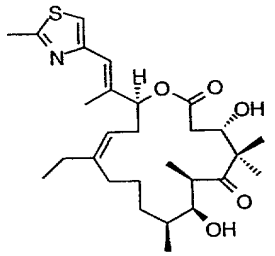
22
(0.098)
[0.146]



23

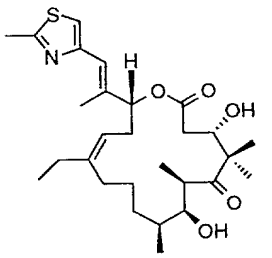


24
(0.0043)
[0.032]

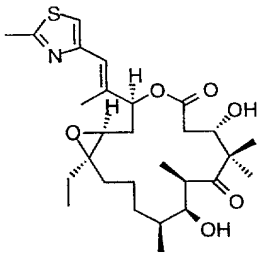


25
(0.021)
[0.077]

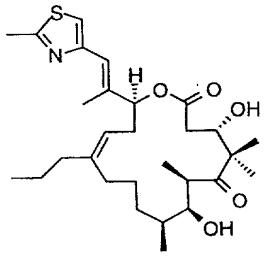
Fig. 41



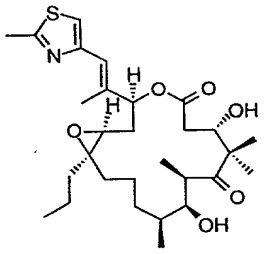
26
(0.055)
[0.197]



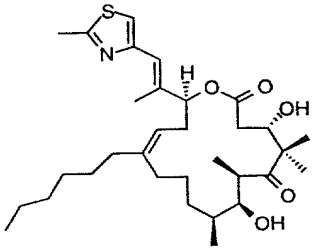
27
(0.0010)
[0.0072]



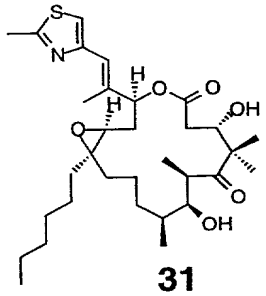
28
(0.039)
[0.067]



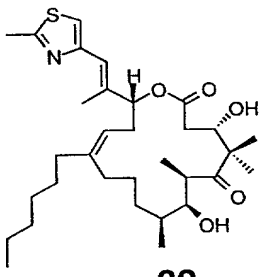
29
(0.0038)
[0.0064]



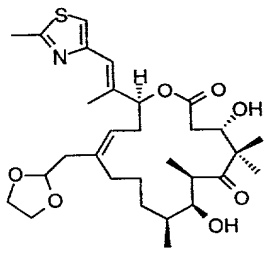
30
(0.044)
[0.108]



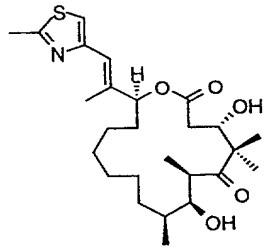
31
(0.027)
[0.049]



32
(0.063)
[0.380]



33
(0.0031)
[0.0093]



34
(0.143)
[0.276]

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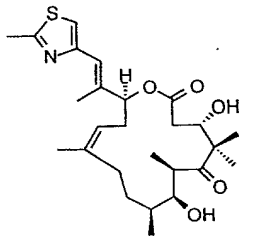
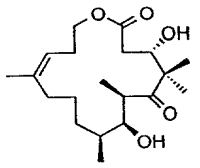
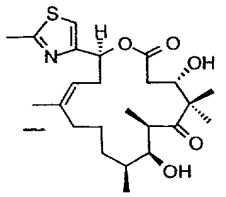
Fig. 42(A)



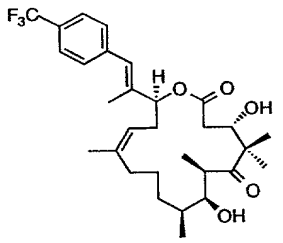
35
(>10)
[8.95]



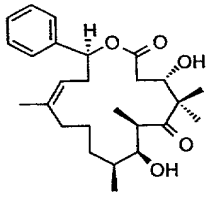
36
(234.5)
[>10]



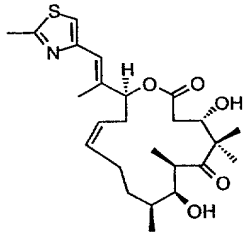
37
(3.25)
[1.20]



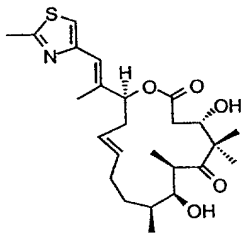
38
(0.254)
[>5.0]



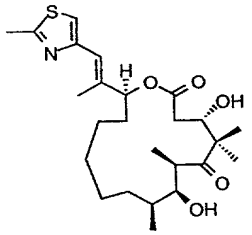
39
(1.80)
[>5.0]



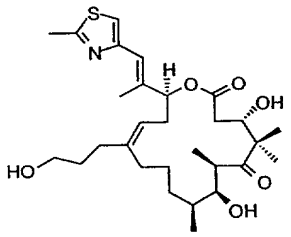
40
(36.9)
[47.3]



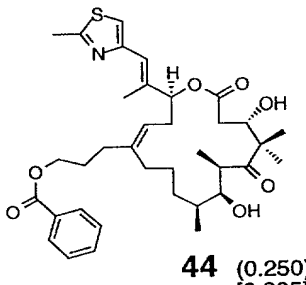
41
(60.1)
[59.2]



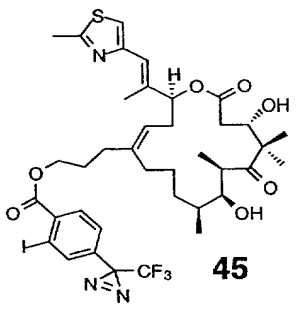
42
(7.41)
[12.9]



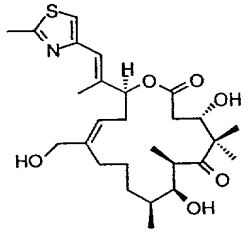
43
(0.0095)
[0.167]



44 (0.250)
[0.905]

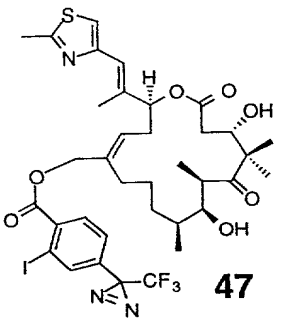


45

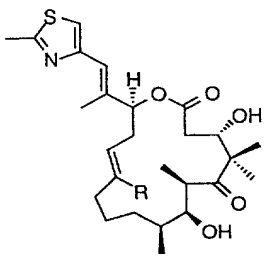


46 (0.049)
[>1.0]

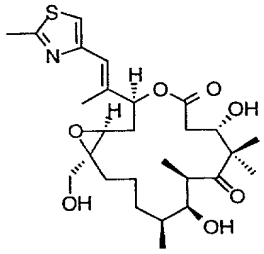
Fig. 42(B)



47



48 R = $(CH_2)_3OH$



49

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Fig. 42(C)

Fig. 43(A)

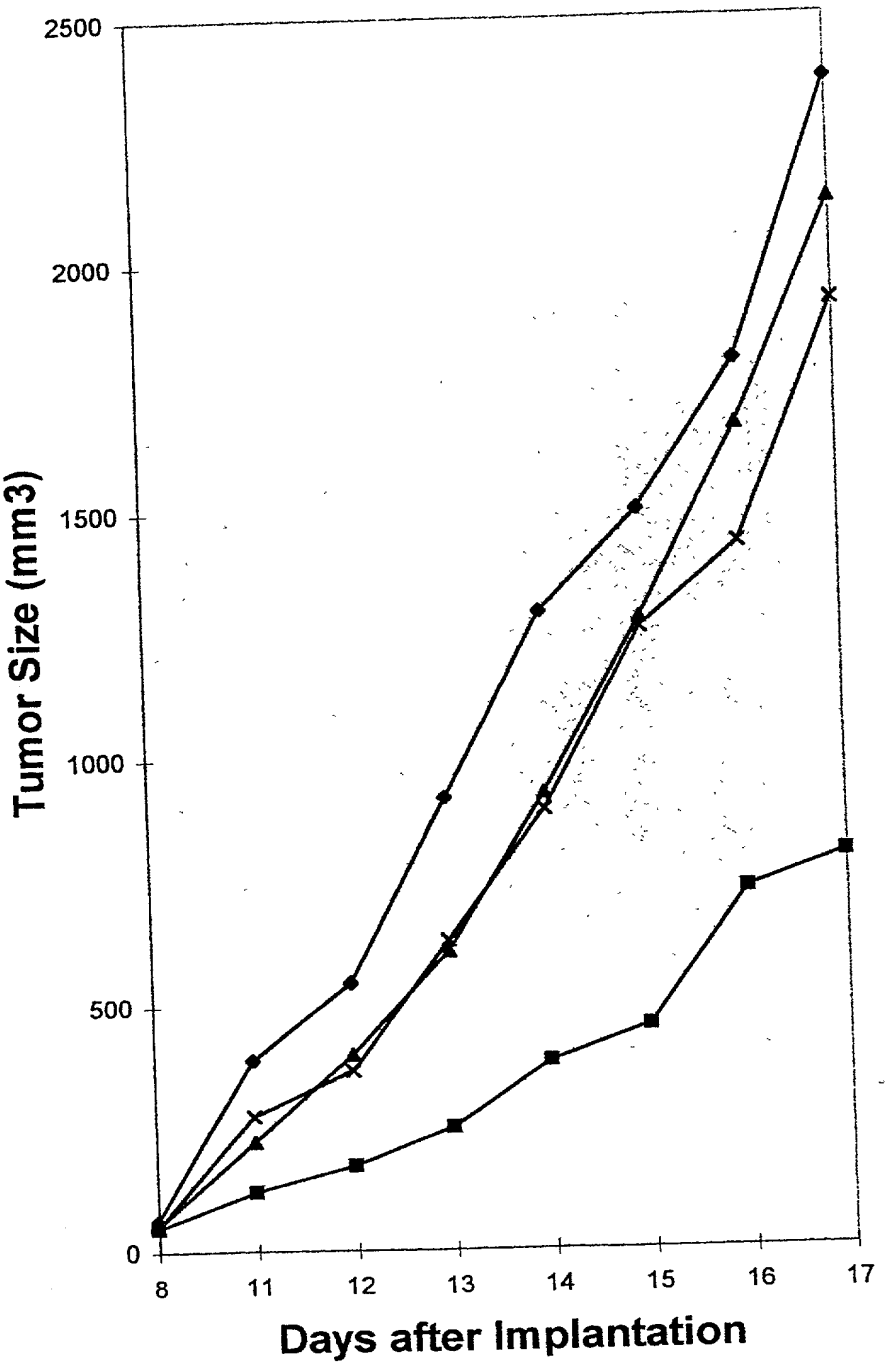
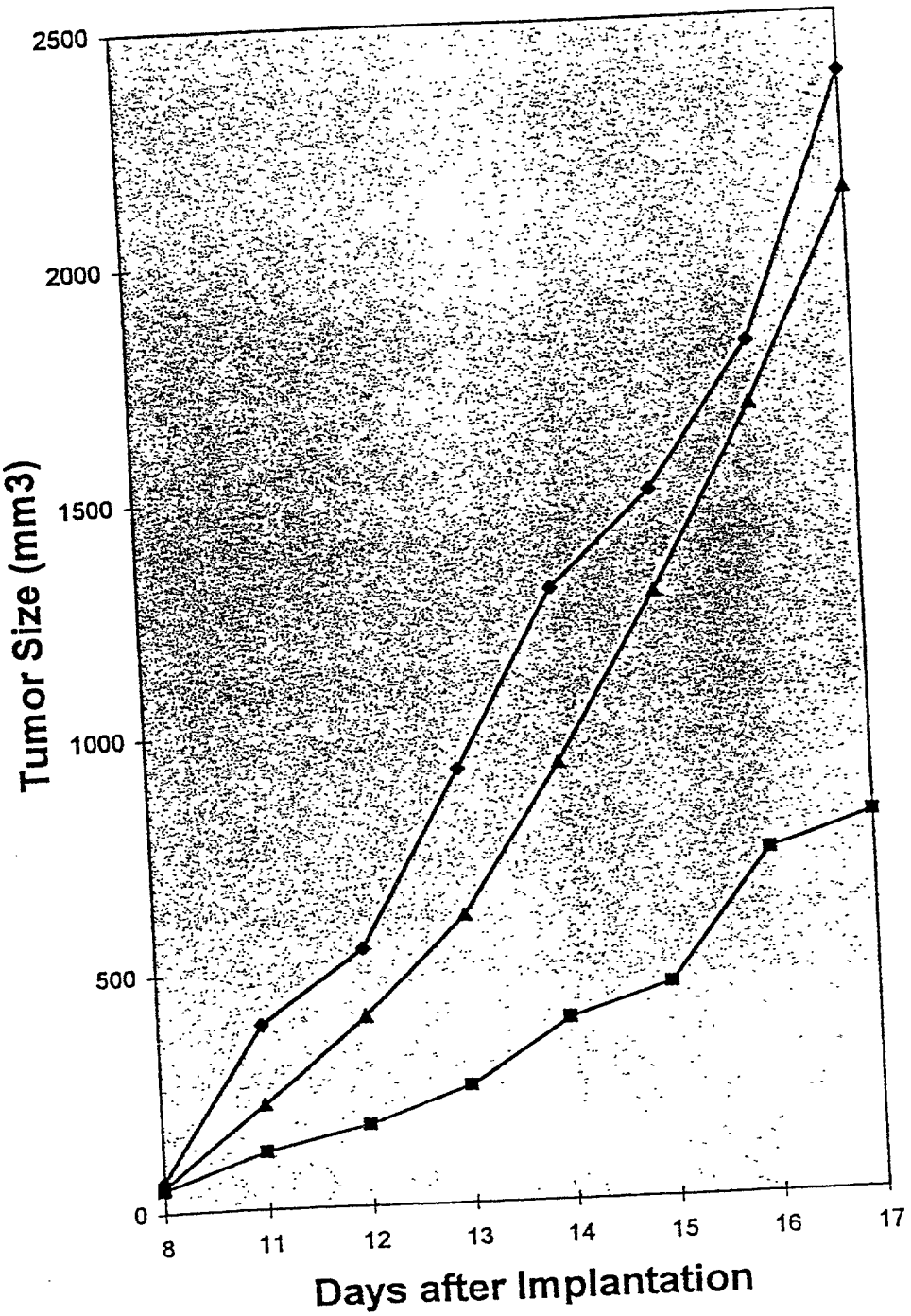

2500
2000
1500
1000
500
0
Tumor Size (mm3)
8
11
12
13
14
15
16
17
Days after Implantation

Fig. 43(B)


2500
2000
1500
1000
500
0
Tumor Size (mm3)
8
11
12
13
14
15
16
17
Days after Implantation

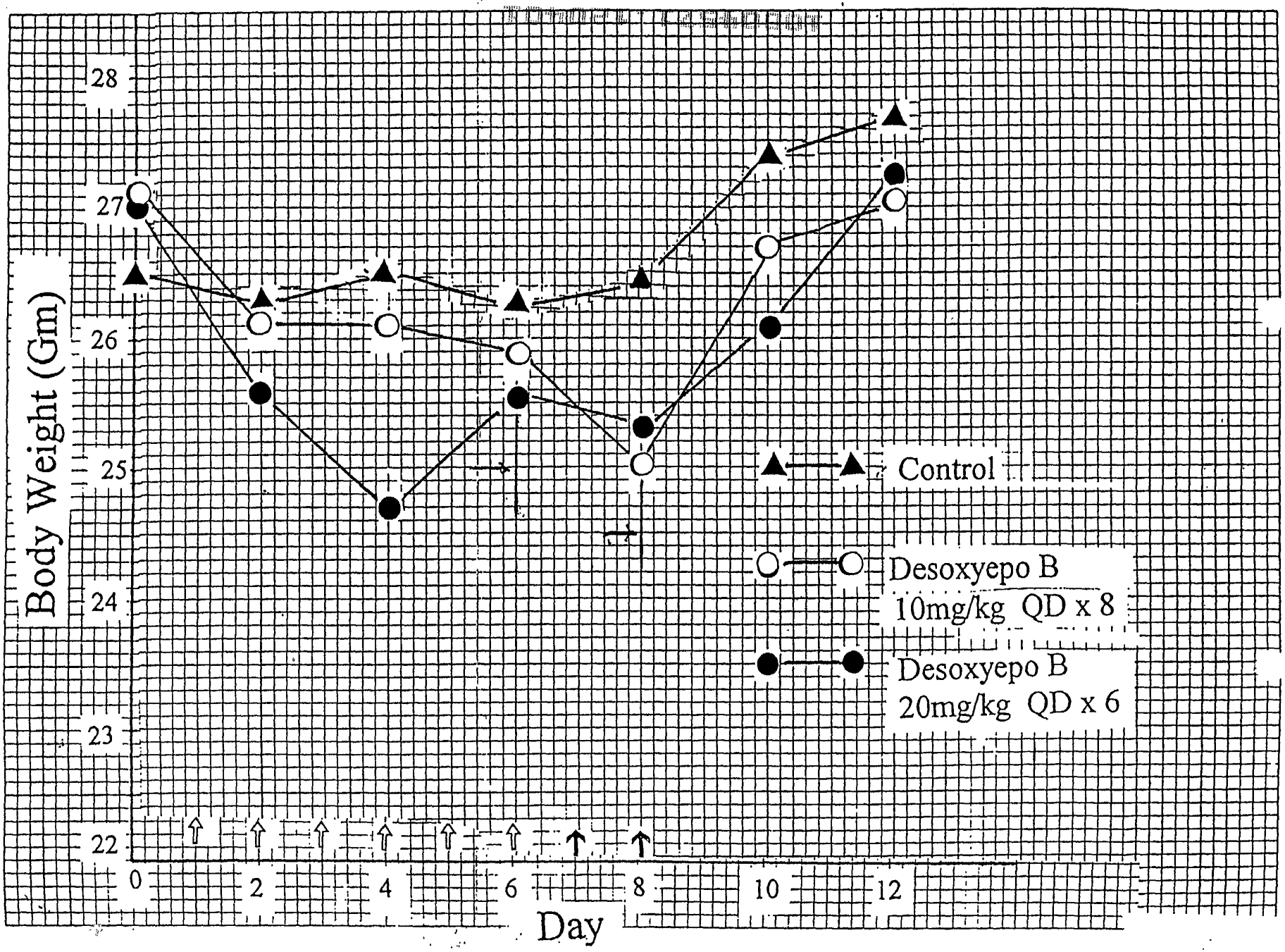

Body Weight (Gm)
28
27
26
25
24
23
22
0
2
4
6
8
10
12
Day
Control
Desoxyepo B
10mg/kg QD x 8
Desoxyepo B
20mg/kg QD x 6

Fig. 44(A)

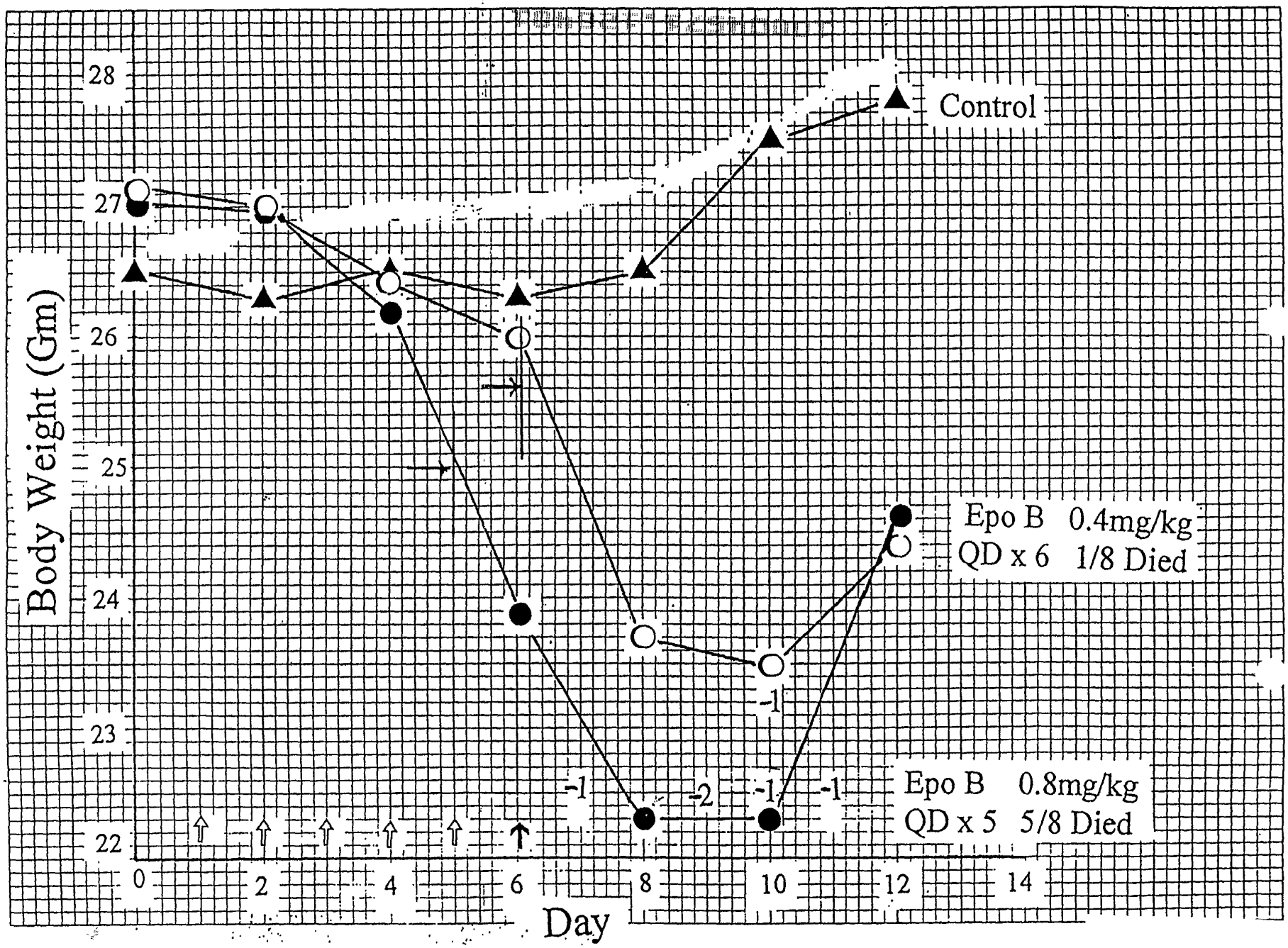

Body Weight (Gm)
28
27
26
25
24
23
22
0
2
4
6
8
10
12
14
Day
Control
Epo B 0.4mg/kg
QD x 6 1/8 Died
Epo B 0.8mg/kg
QD x 5 5/8 Died
-1
-2
-1
-1
-1

Fig. 44(B)

Fig. 45(A)

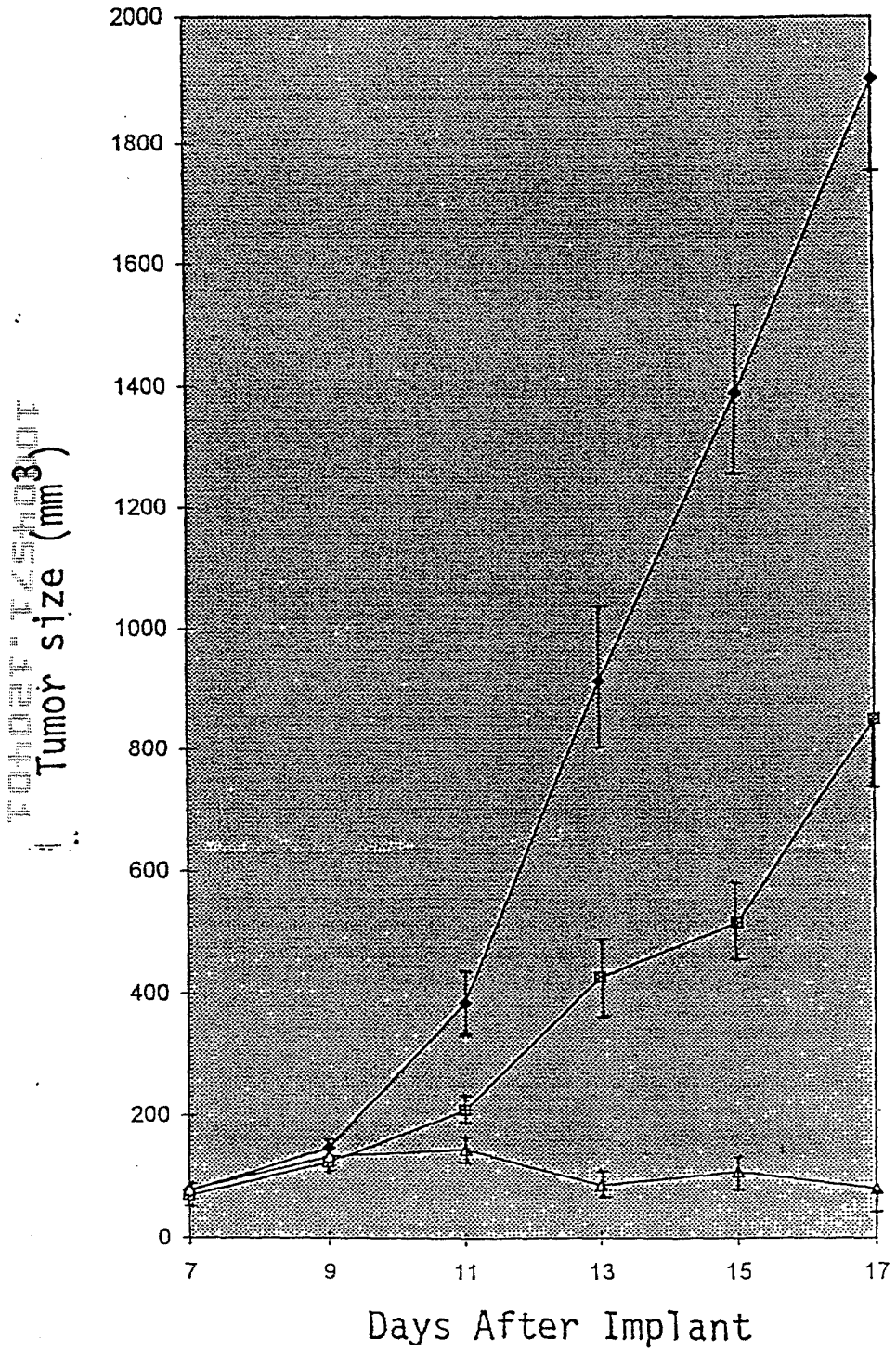
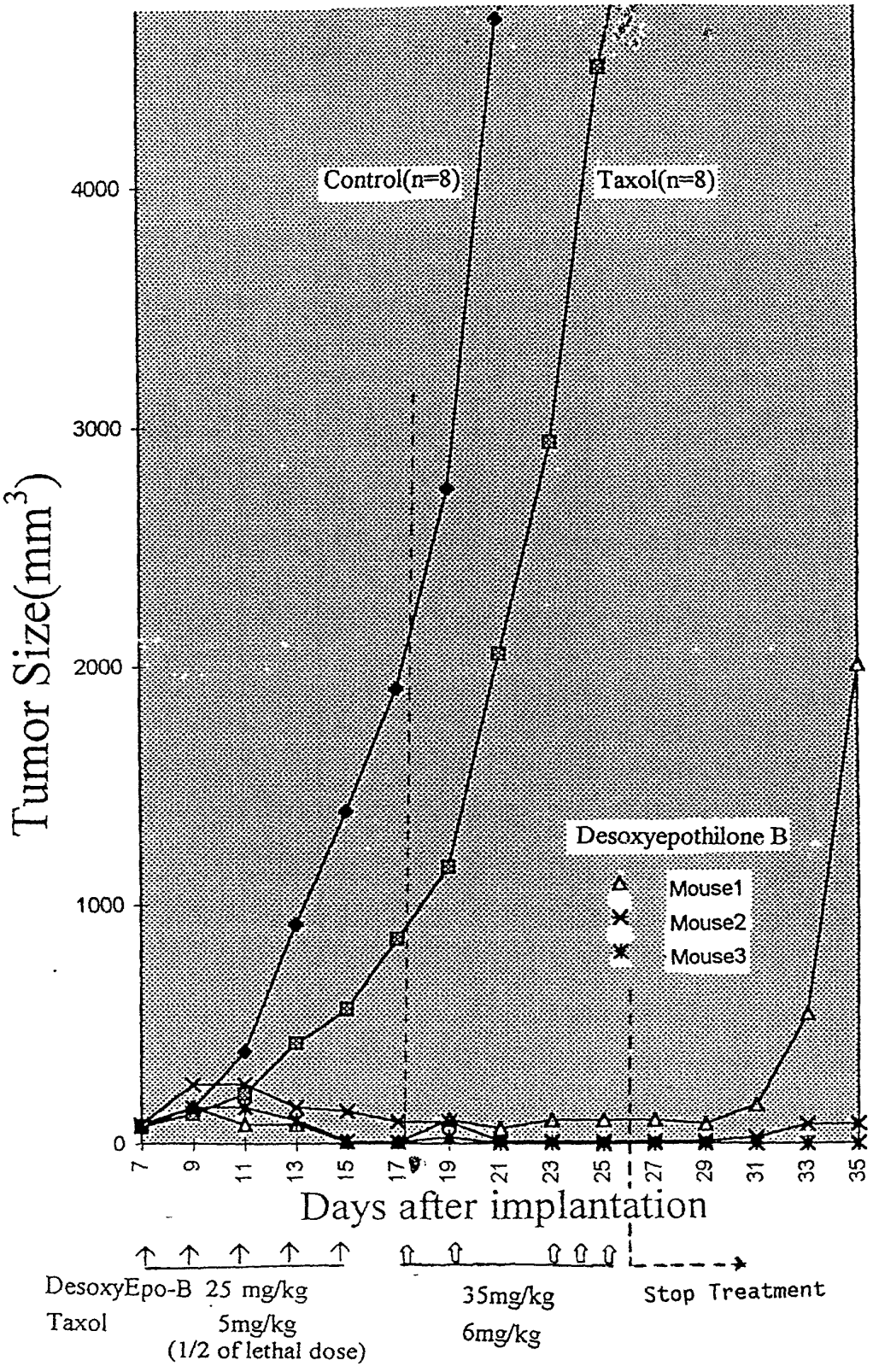

2000
1800
1600
1400
1200
1000
800
600
400
200
0
Tumor size (mm3)
7
9
11
13
15
17
Days After Implant

Fig. 45(B)


Control(n=8)
Taxol(n=8)
Desoxyepothilone B
Mouse1
Mouse2
Mouse3
Tumor Size(mm3)
Days after implantation
DesoxyEpo-B 25 mg/kg
Taxol 5mg/kg
(1/2 of lethal dose)
35mg/kg
6mg/kg
Stop Treatment

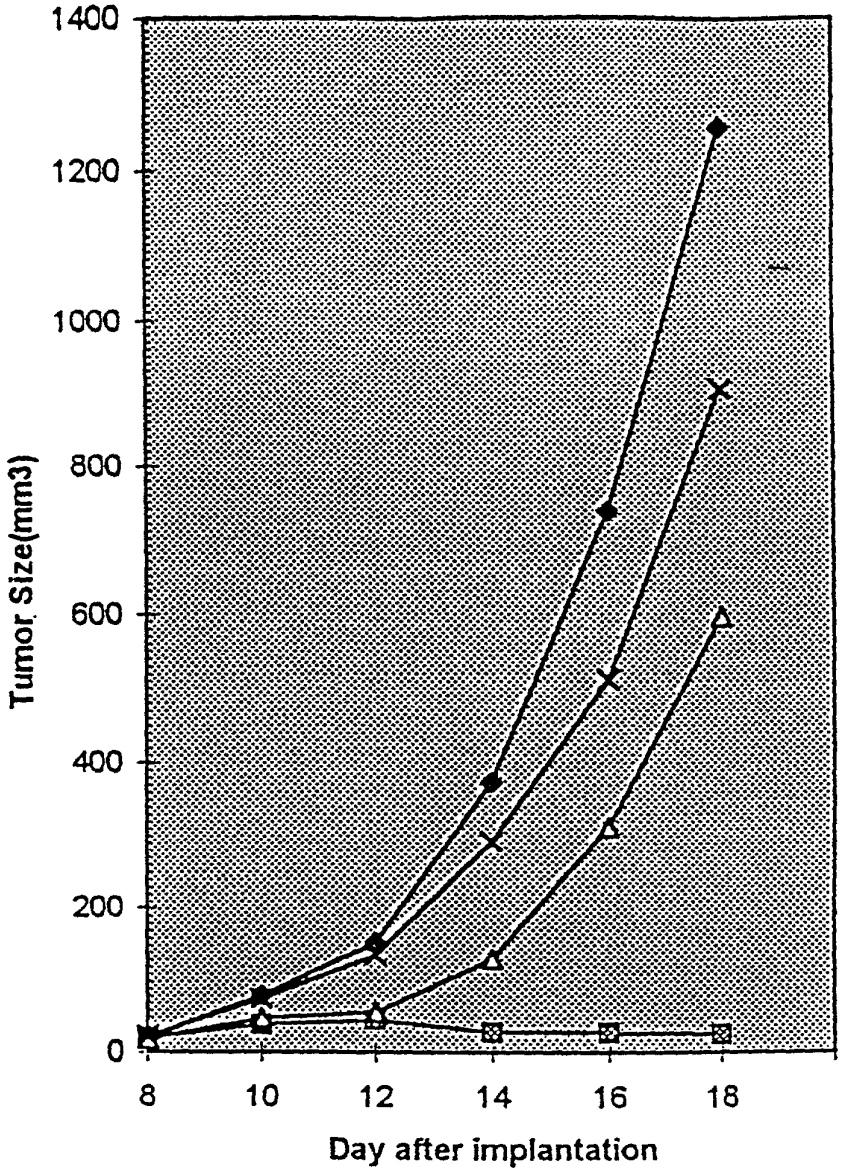
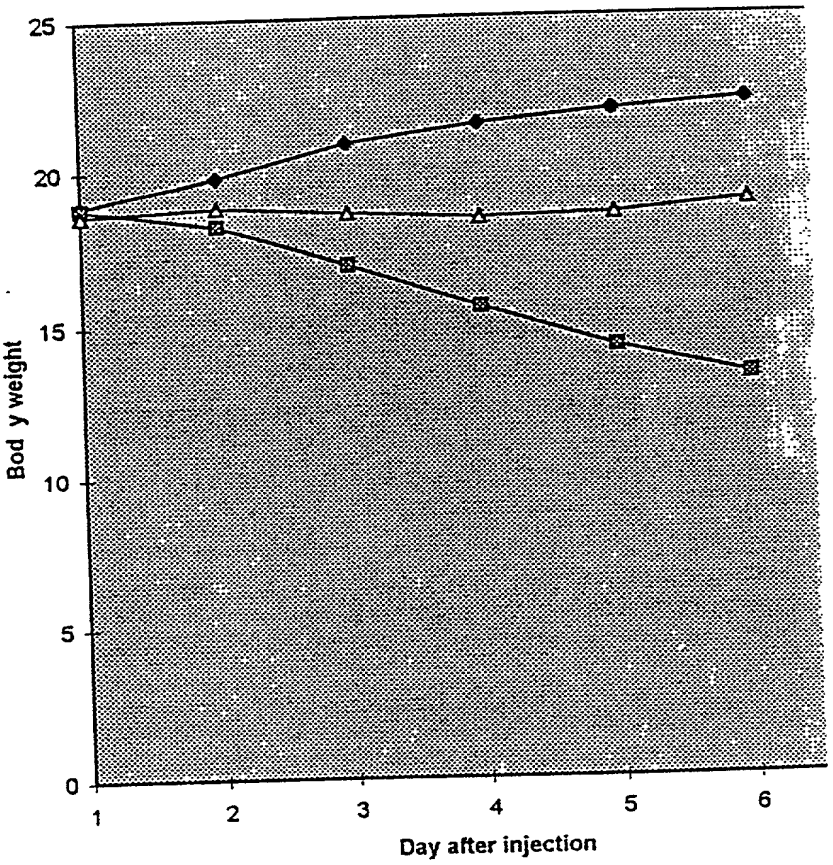
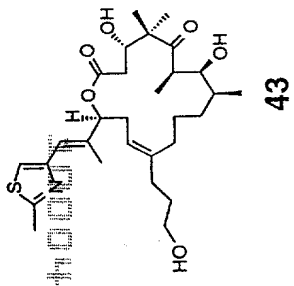

1400
1200
1000
800
600
400
200
0
Tumor Size(mm3)
8
10
12
14
16
18
Day after implantation

Fig. 46

Fig. 47





43

400 MHz, cdcl3, rt,

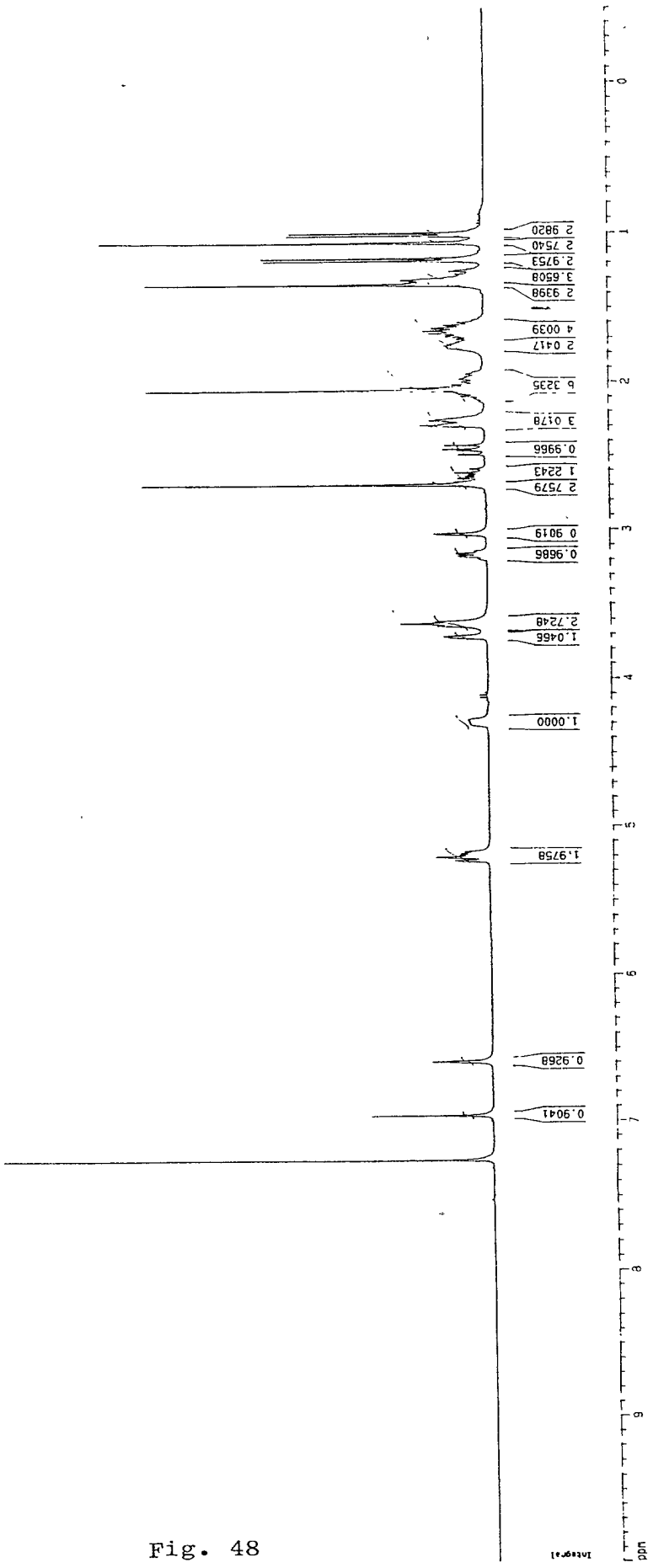


Fig. 48

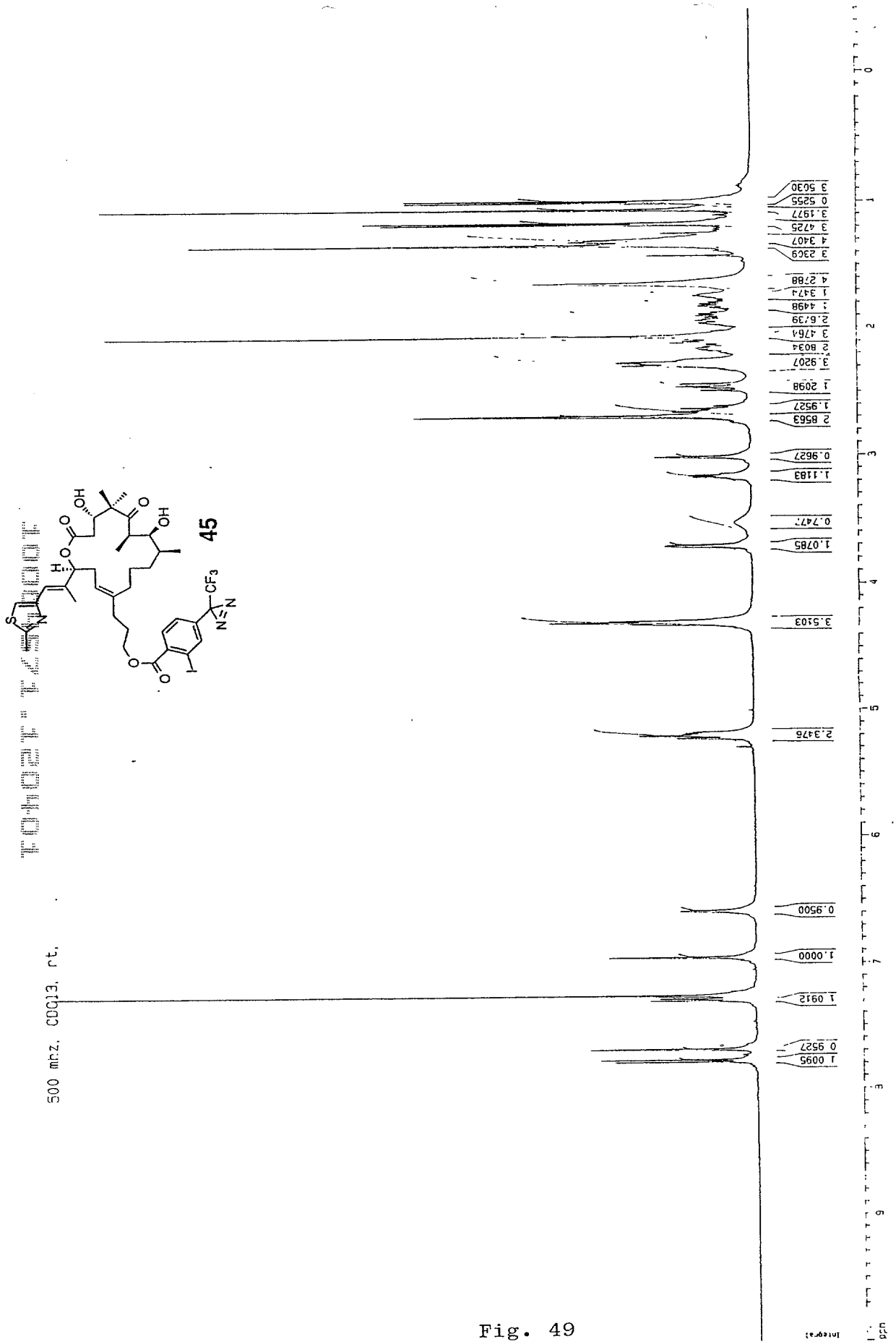

500 mHz, CDCl3, rt.
45
3.5030
0.9255
3.1977
3.4725
4.3407
3.2369
4.2788
1.3474
3.4984
2.6739
3.4764
2.8034
3.9207
1.2098
1.9527
2.8563
0.9827
1.1183
0.7477
1.0785
3.5103
2.3476
0.9500
1.0000
1.0912
0.9527
1.0095
Integral
ppm

Fig. 49

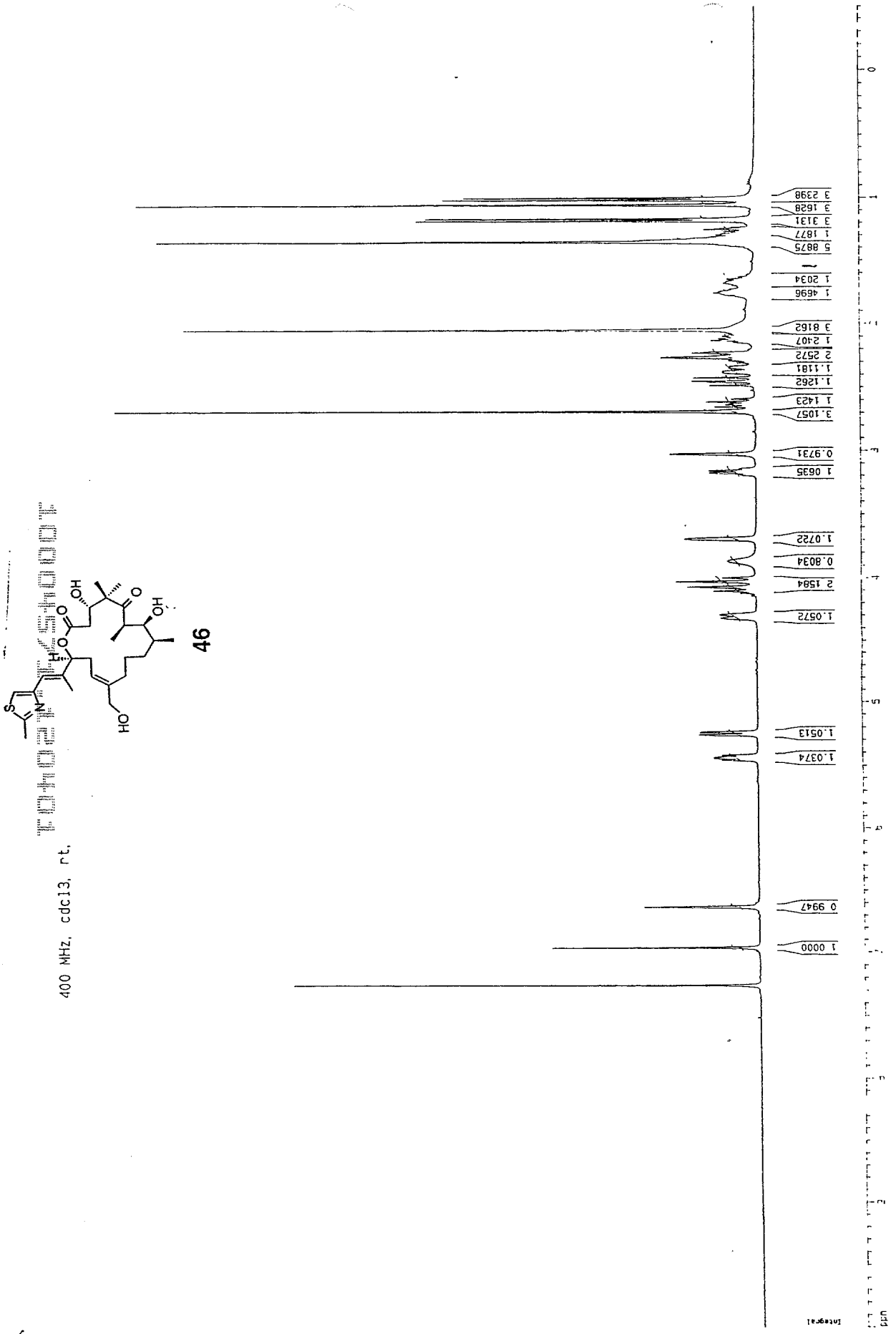

400 MHz, cdcl3, rt.
46
OH
O
OH
O
O
H
S
N
HO
Integral
3 2398
3 1628
3 3131
1 1877
5 8875
1 2034
1 4696
3 8162
1 2407
2 2572
1.1184
1.1262
1 1423
3.1057
0.9731
1 0635
1.0722
0.8034
2 1584
1.0572
1.0513
1.0374
0 9947
1 0000

Fig. 50

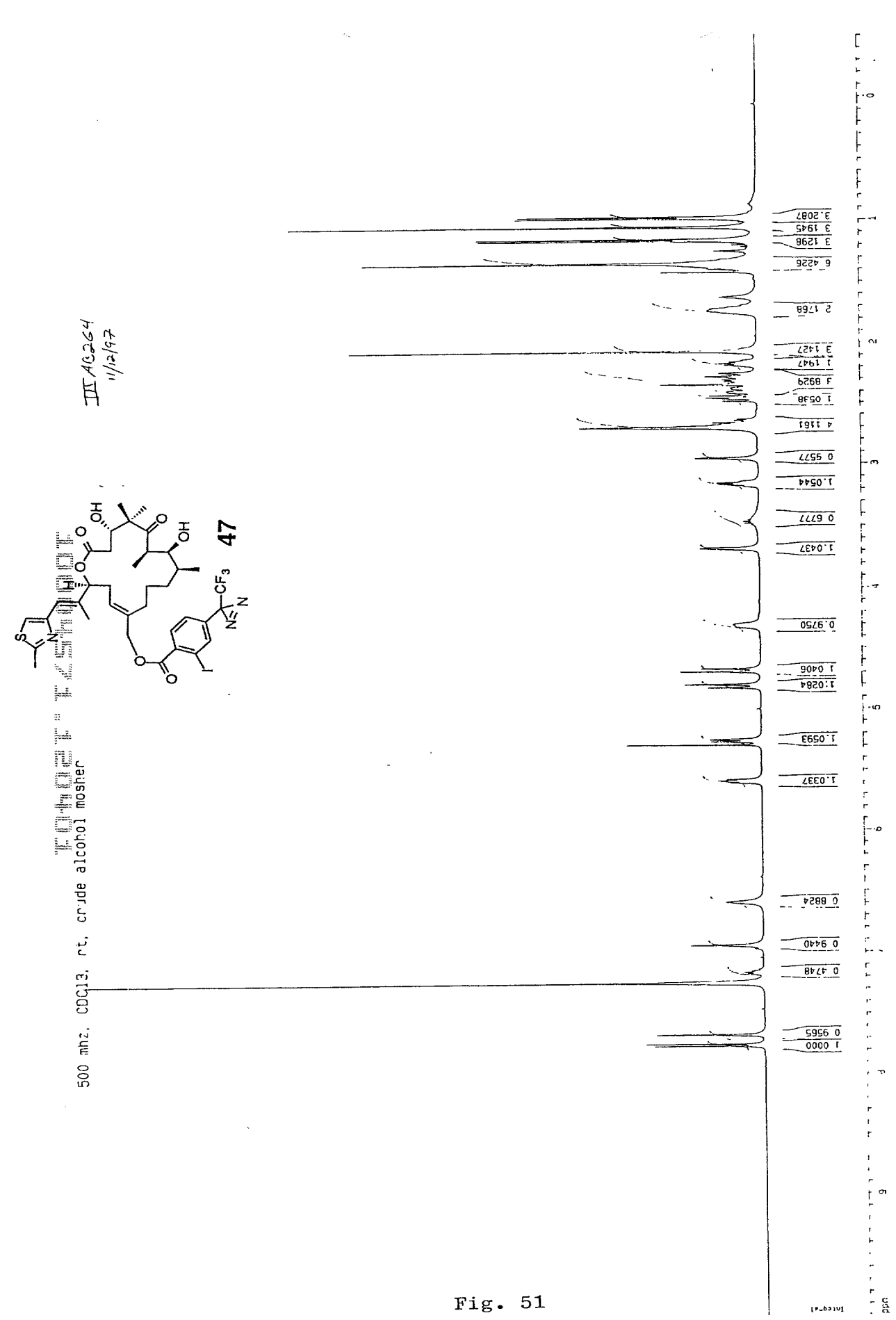

500 mhz, CDCl3, rt, crude alcohol mosher
47
IIIA13264
11/12/97
3.2087
3.1945
3.1298
6.4226
2.1768
3.1427
1.1947
3.8929
1.0538
4.1161
0.9577
1.0544
0.6777
1.0437
0.9750
1.0406
1.0284
1.0593
1.0337
0.8824
0.9440
0.4748
0.9565
1.0000

Fig. 51

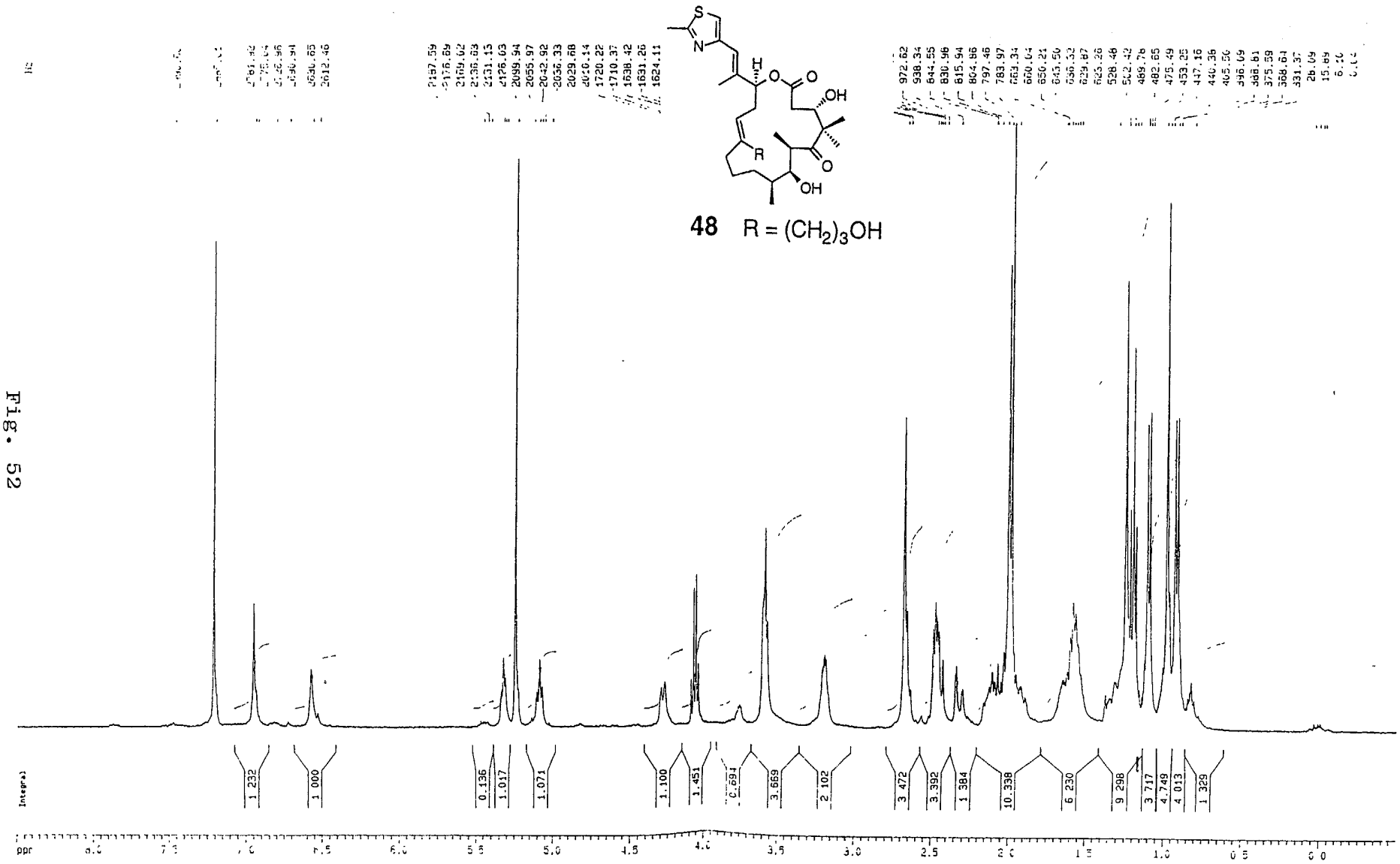


Fig. 52

FIG. 1A

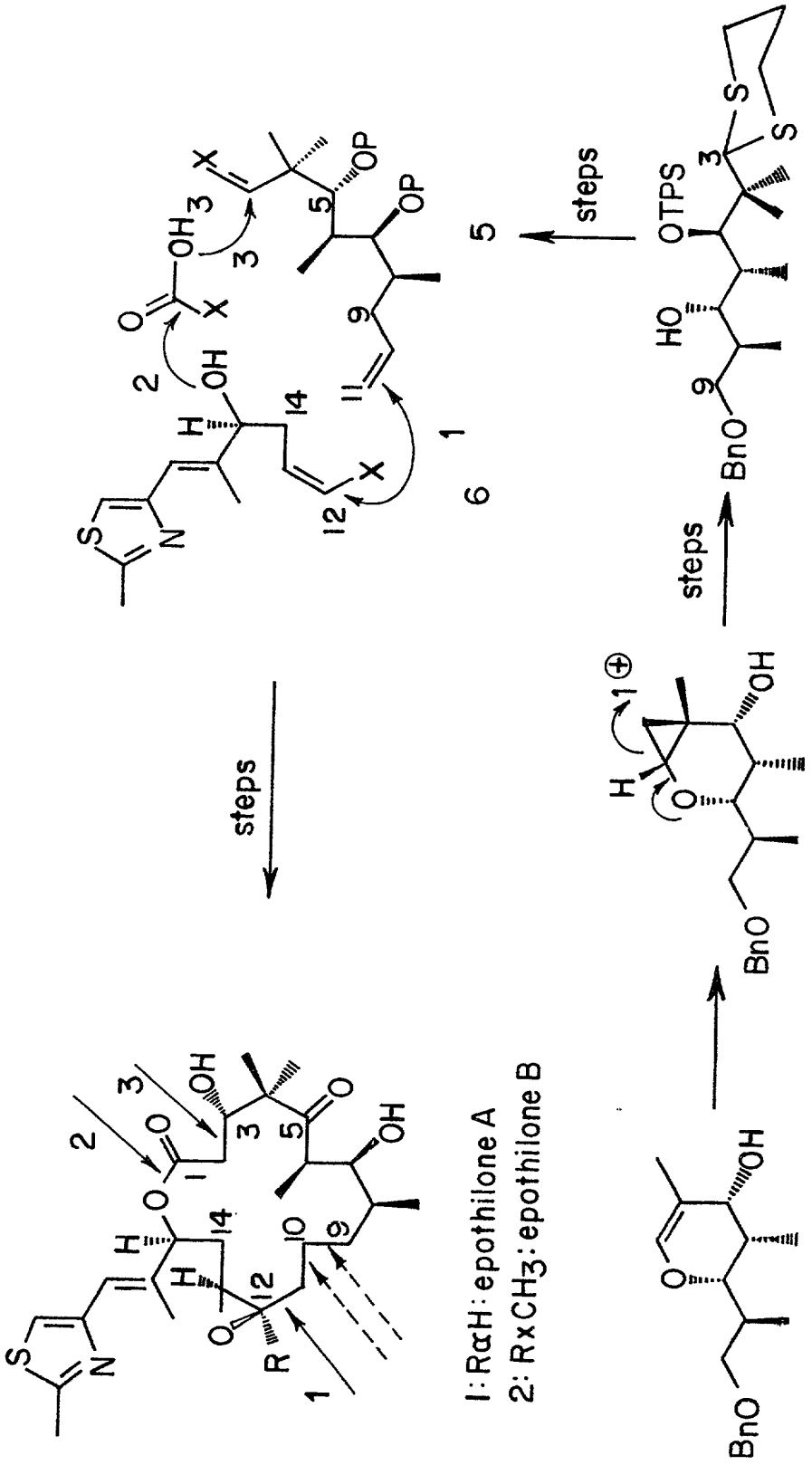


FIG. 1B

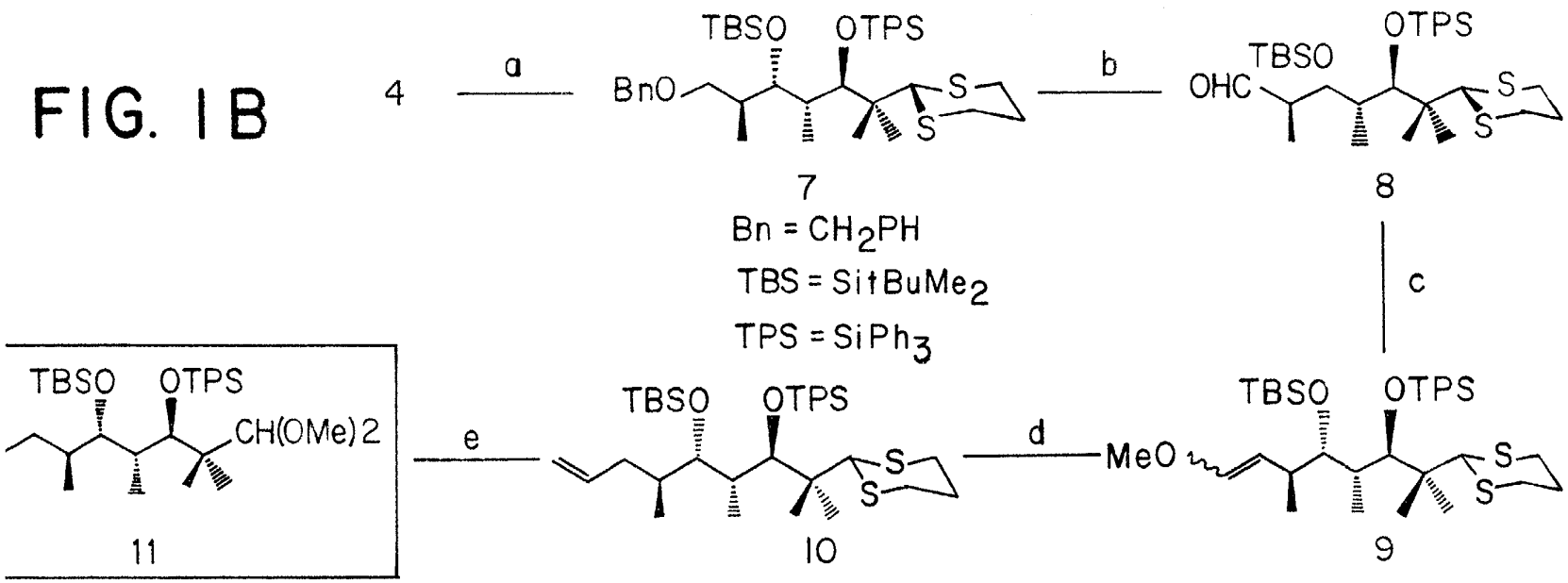
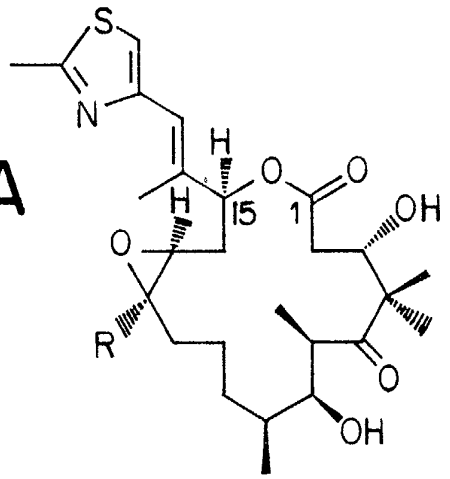
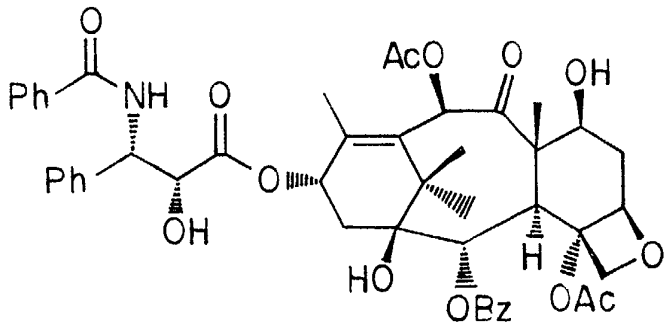


FIG. 12A



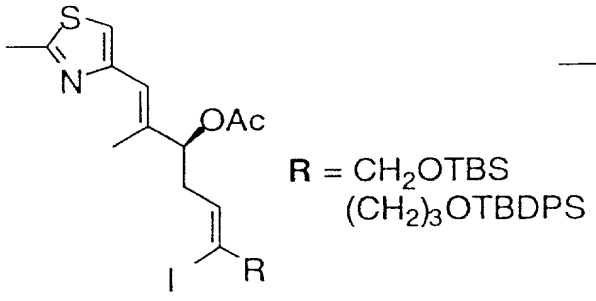
R= H: epothilone A
R= CH_3: epothilone B

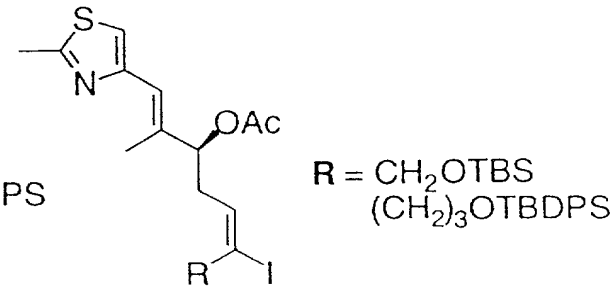
FIG. 12B

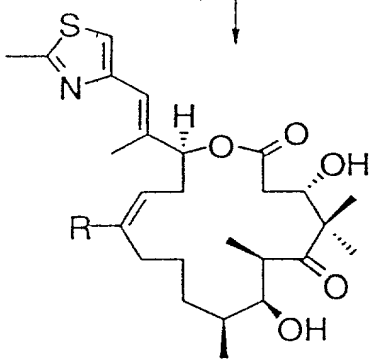


1A: taxol™

FIG. 2

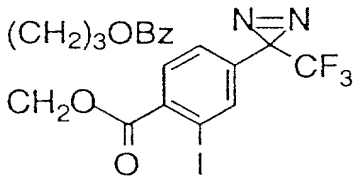


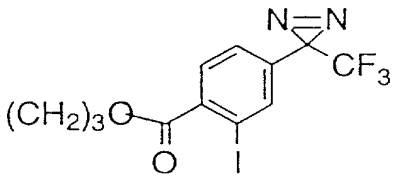


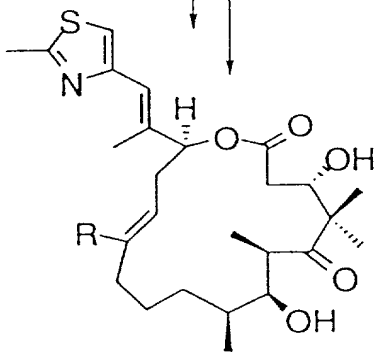


R = CH_2OH

$(CH_2)_3OH$







R = CH_2OH
$(CH_2)_3OH$

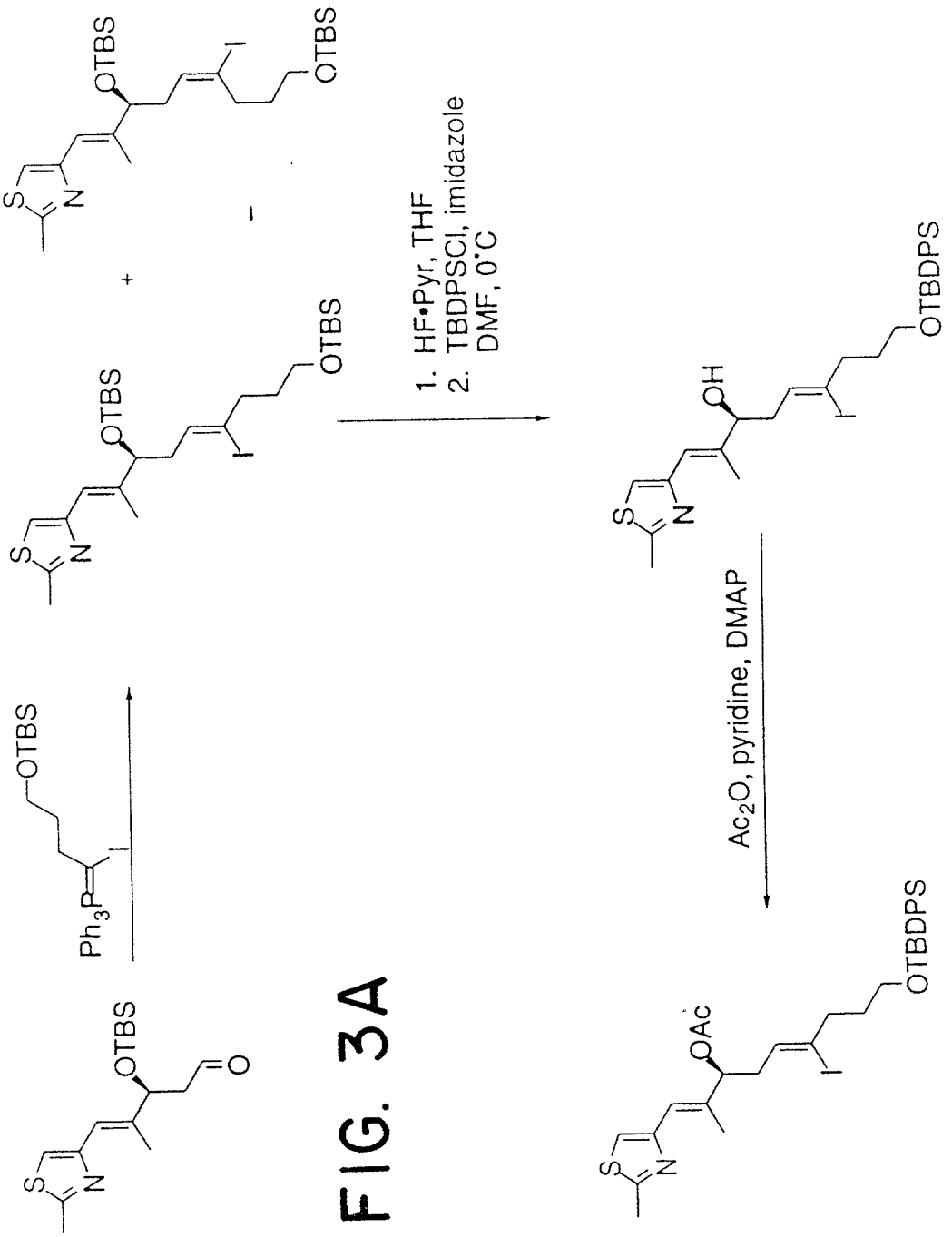

OTBS
O
Ph_3P
I
1. HF•Pyr, THF
2. TBDPSCl, imidazole
DMF, 0°C
OH
OTBDPS
Ac_2O, pyridine, DMAP
OAc

FIG. 3A

FIG. 3B

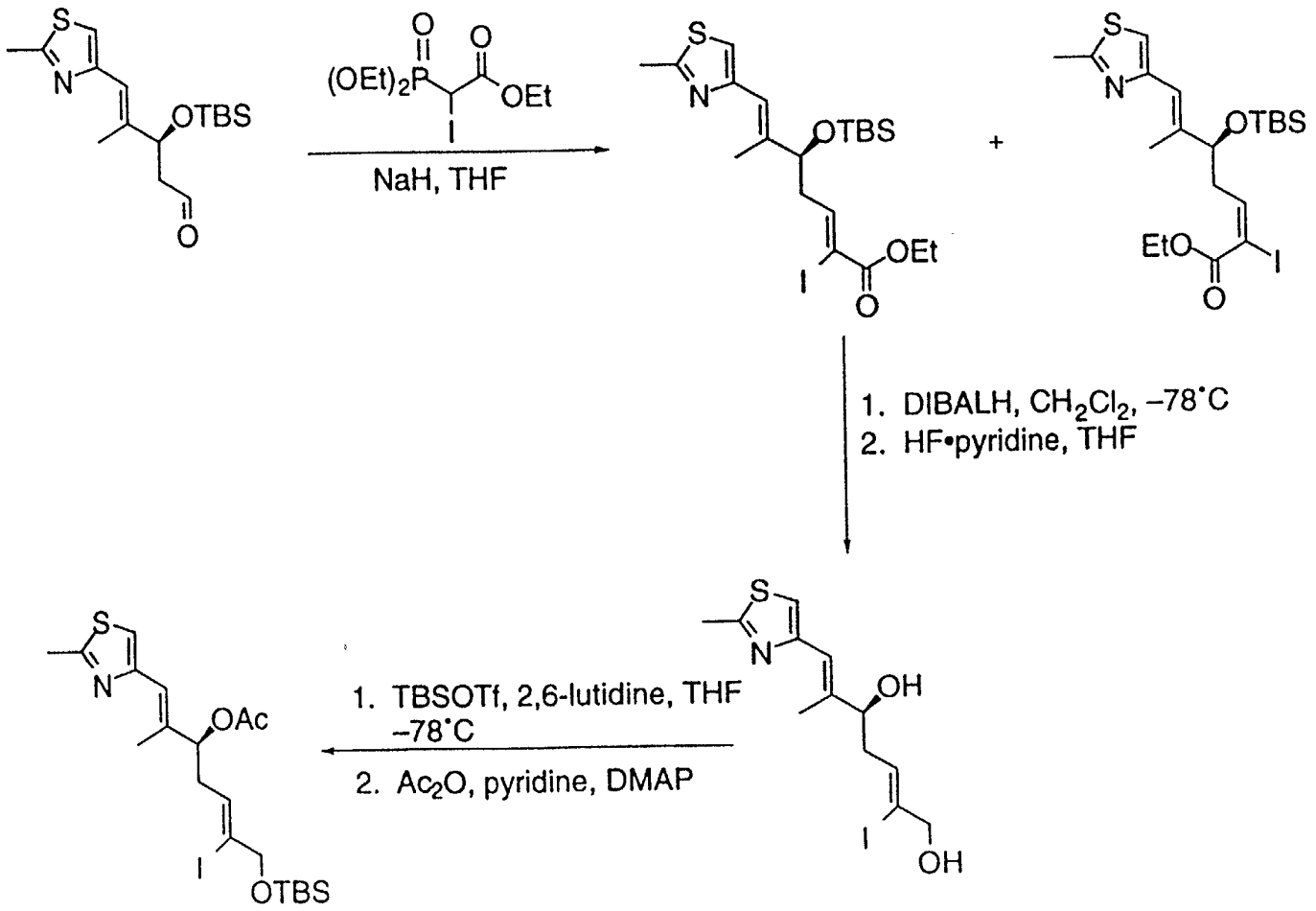
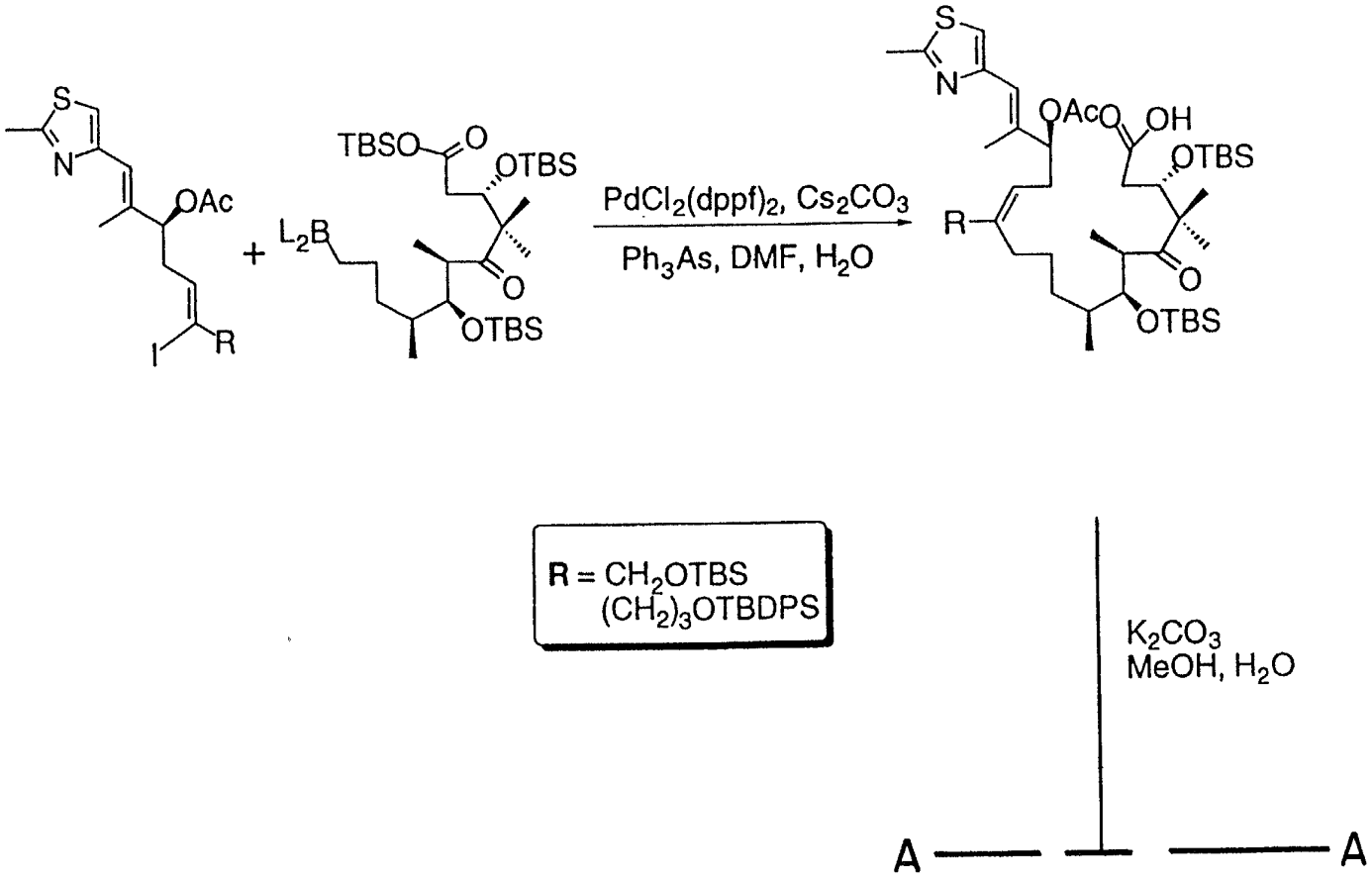

S
N
OTBS
O
(OEt)2P
O
OEt
I
NaH, THF
OTBS
OEt
I
O
+
EtO
1. DIBALH, CH2Cl2, –78°C
2. HF•pyridine, THF
OH
OH
1. TBSOTf, 2,6-lutidine, THF
–78°C
2. Ac2O, pyridine, DMAP
OAc
OTBS

FIG. 3C


S
N
OAc
I
R
+
L2B
TBSO
O
OTBS
O
OTBS
PdCl2(dppf)2, Cs2CO3
Ph3As, DMF, H2O
S
N
OAcO
OH
OTBS
R
O
OTBS
R = CH2OTBS
(CH2)3OTBDPS
K2CO3
MeOH, H2O
A
A

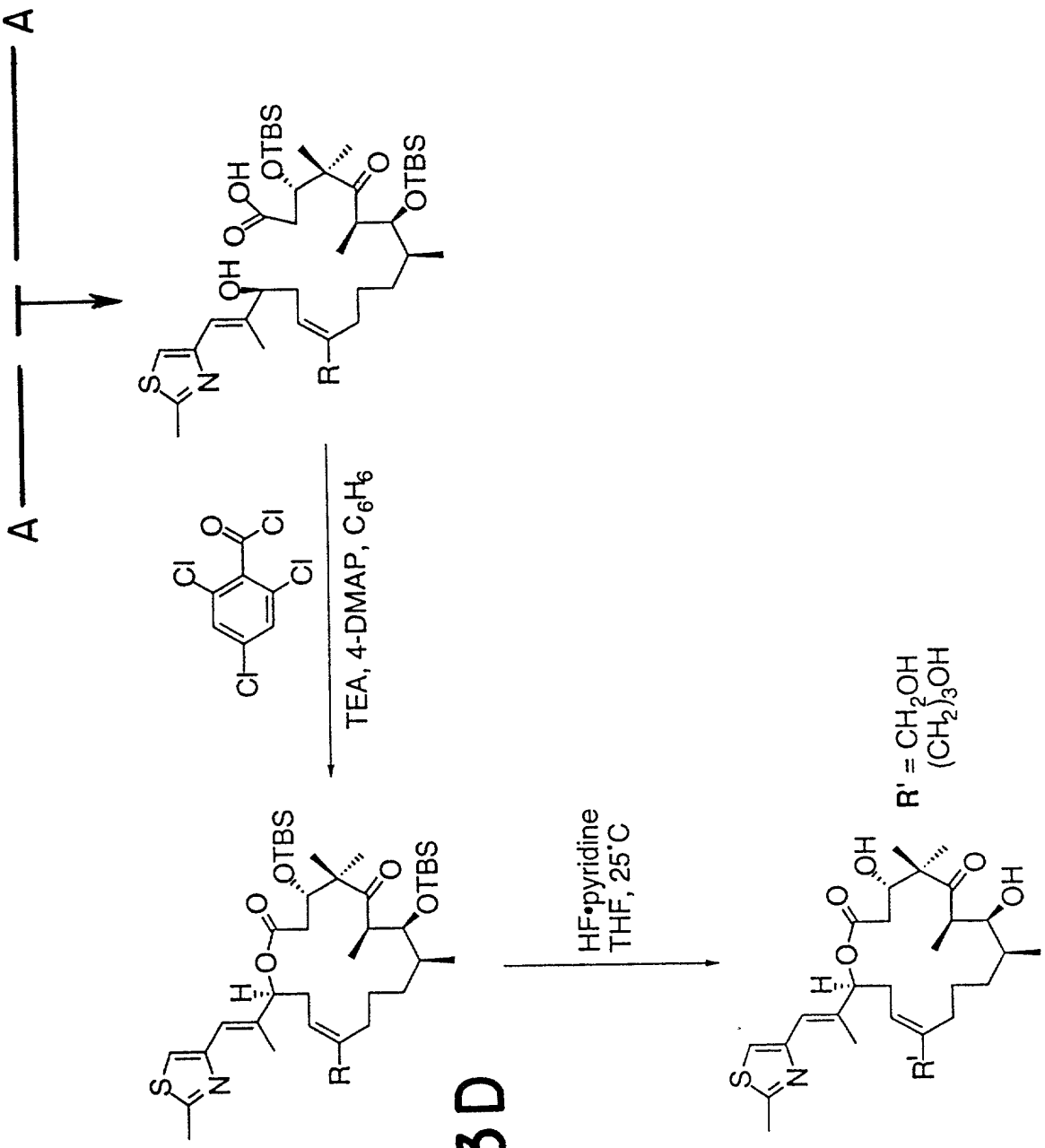

A
A
OTBS
OH
O
OH
O
OTBS
S
N
R
Cl
Cl
Cl
Cl
TEA, 4-DMAP, C_6H_6
OTBS
O
OTBS
O
H
O
S
N
R
HF•pyridine
THF, 25°C
OH
O
OH
O
H
O
S
N
R'
R' = CH_2OH
$(CH_2)_3OH$

FIG. 3D

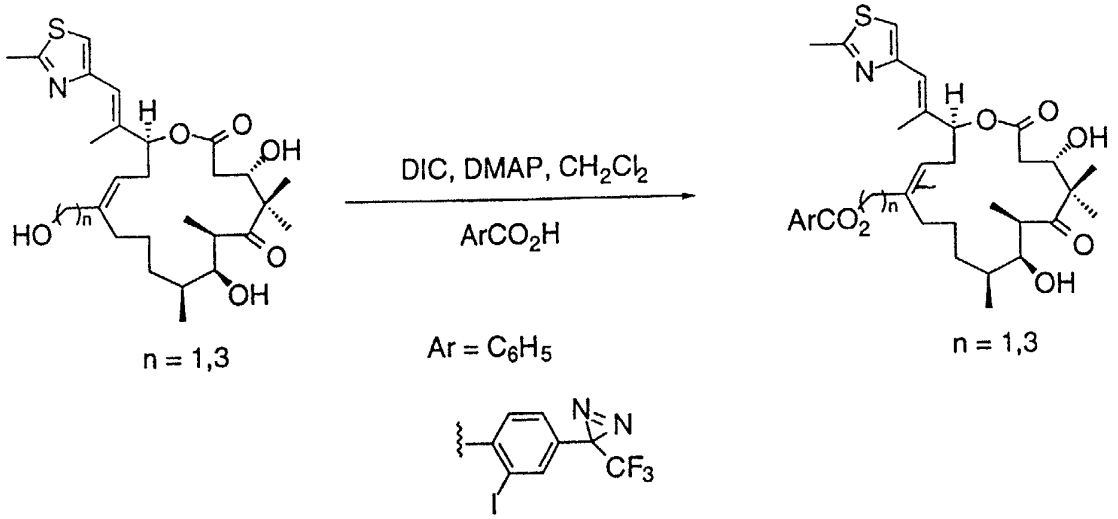


FIG. 3E

FIG. 3F

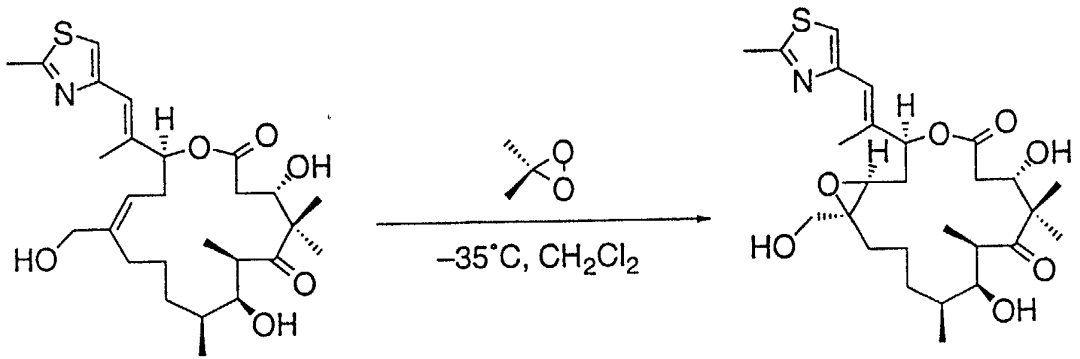


FIG. 4A

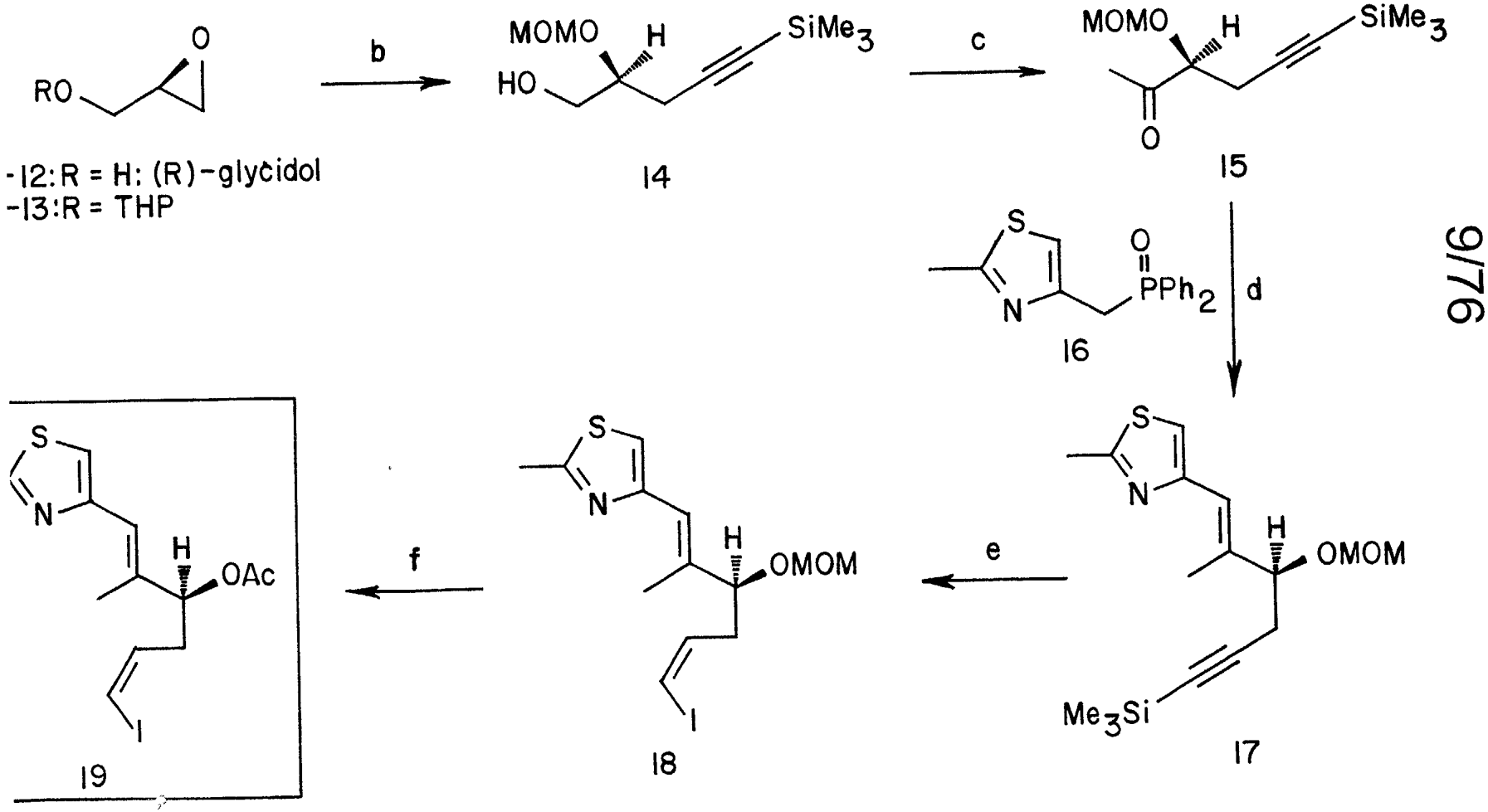

RO
O
b
MOMO
H
HO
SiMe3
c
MOMO
H
SiMe3
O
-12:R = H: (R)-glycidol
-13:R = THP
14
15
S
N
O
PPh2
16
d
S
N
H
OMOM
Me3Si
17
e
S
N
H
OMOM
I
18
f
S
N
H
OAc
I
19

FIG. 4B

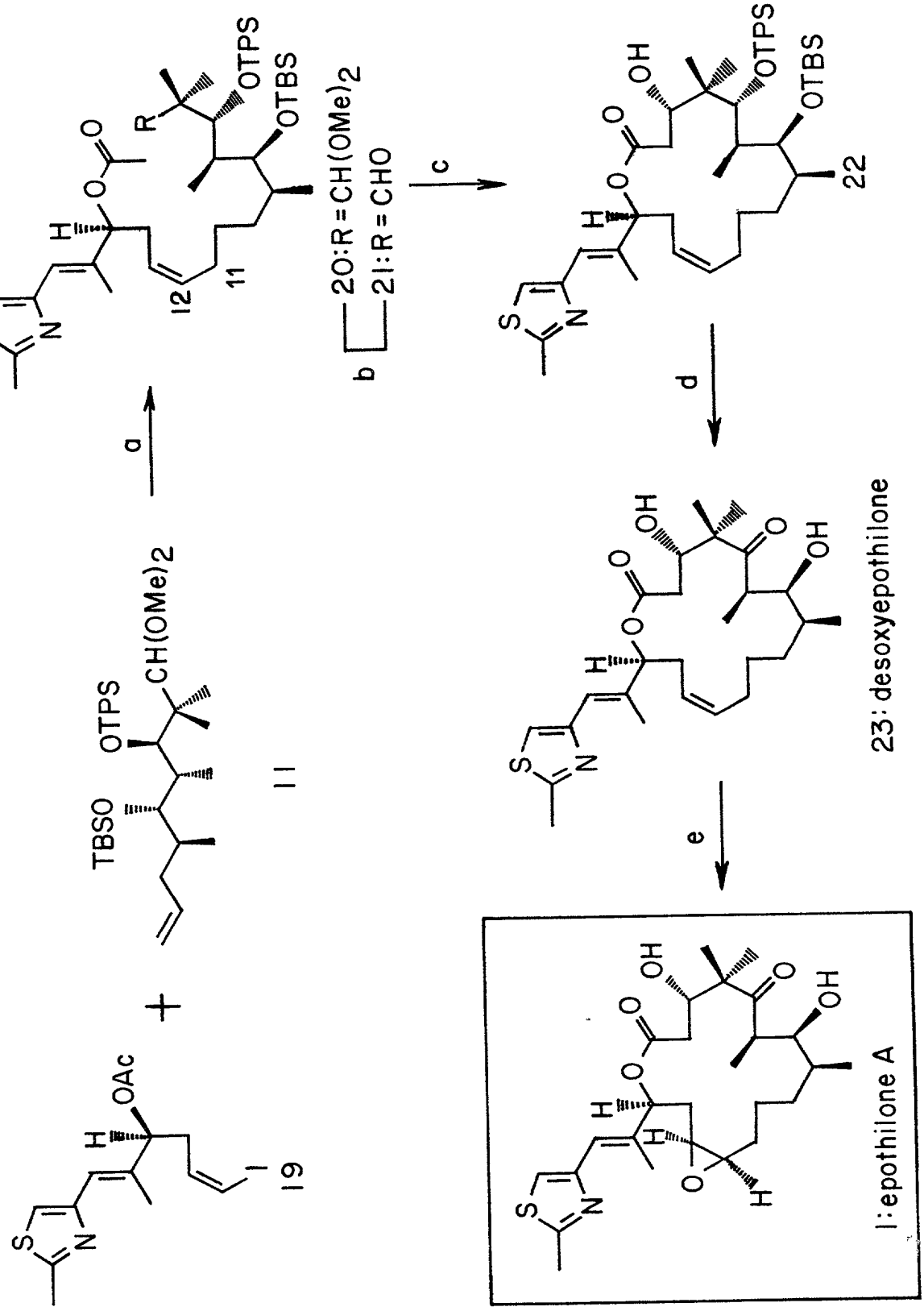

19
11
TBSO
OTPS
CH(OMe)2
OAc
a
20:R=CH(OMe)2
21:R=CHO
b
c
OTBS
OTPS
OH
22
d
23: desoxyepothilone
e
1: epothilone A

FIG. 5

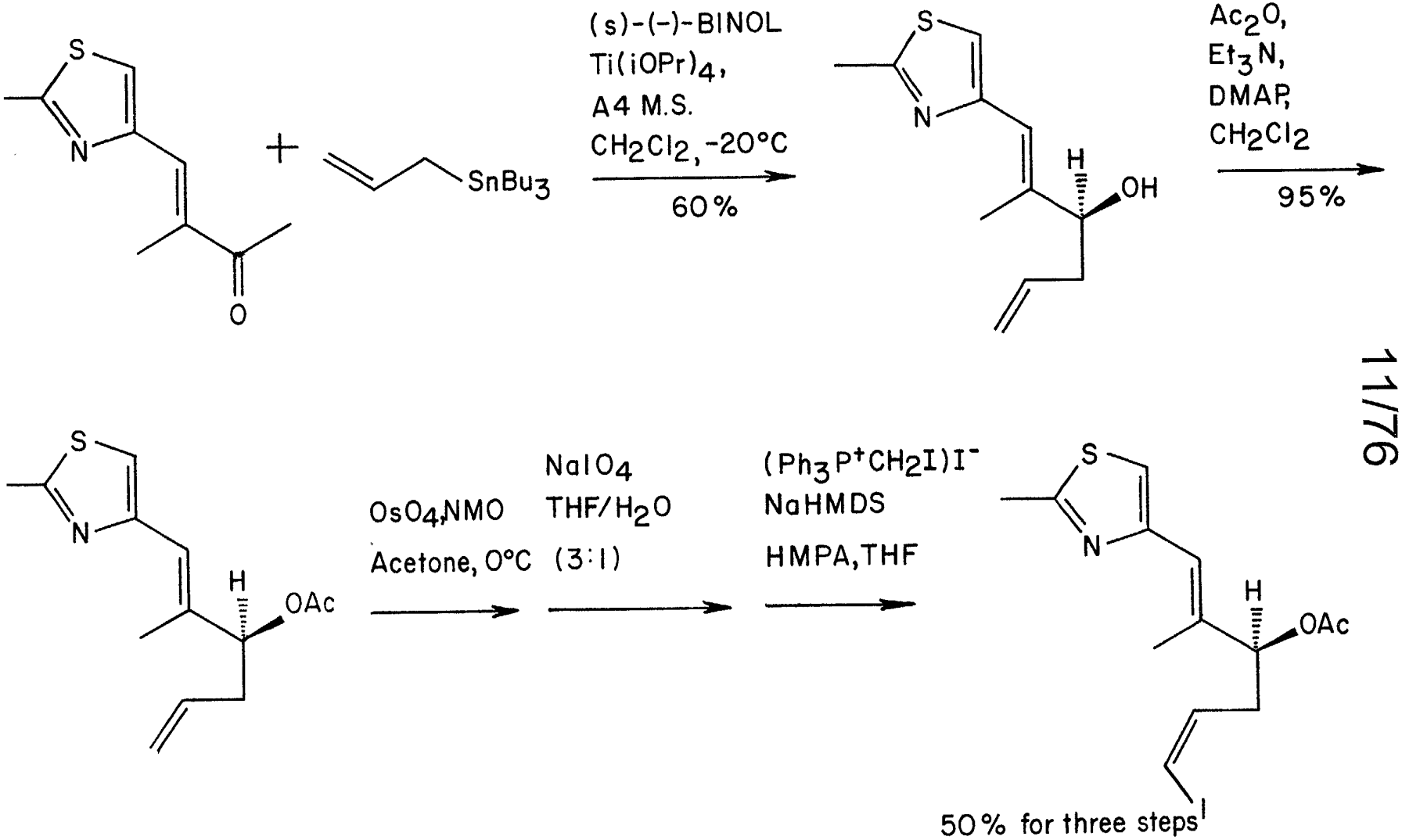

(s)-(-)-BINOL
Ti(iOPr)4,
A4 M.S.
CH2Cl2, -20°C
60%
Ac2O,
Et3N,
DMAP,
CH2Cl2
95%
SnBu3
OH
OAc
OsO4,NMO
Acetone, 0°C
NaIO4
THF/H2O
(3:1)
(Ph3P+CH2I)I-
NaHMDS
HMPA,THF
50% for three steps

FIG. 6A

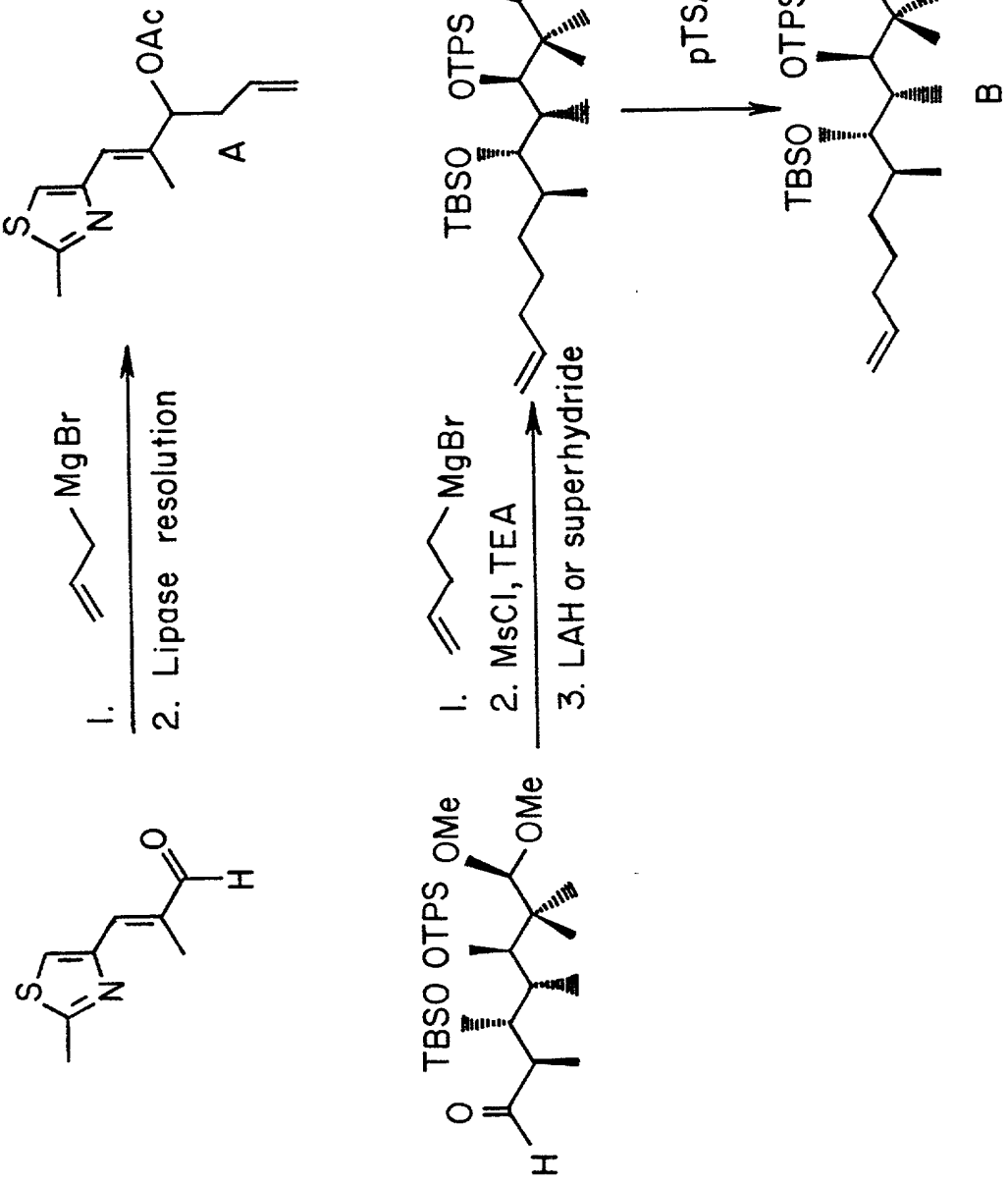
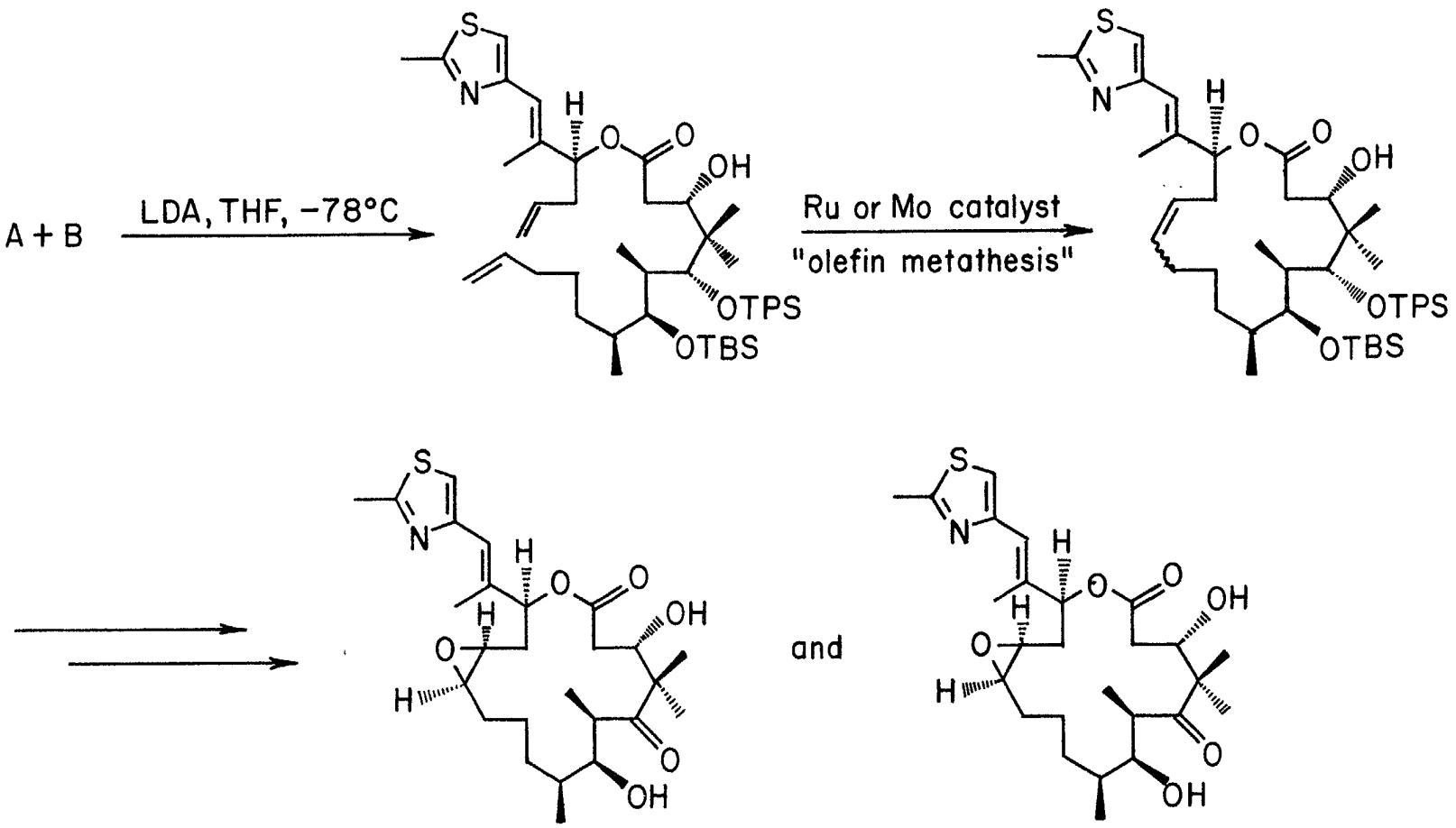

1.
2. Lipase resolution
MgBr
OAc
A
1.
2. MsCl, TEA
3. LAH or superhydride
MgBr
TBSO OTPS OMe OMe
pTSA, H2O
TBSO OTPS O H
B

FIG. 6B



*17 steps from known starting materials vs. 27 steps for aldol macrocyclization

10-May-2007 15:54:00.0

FIG. 7

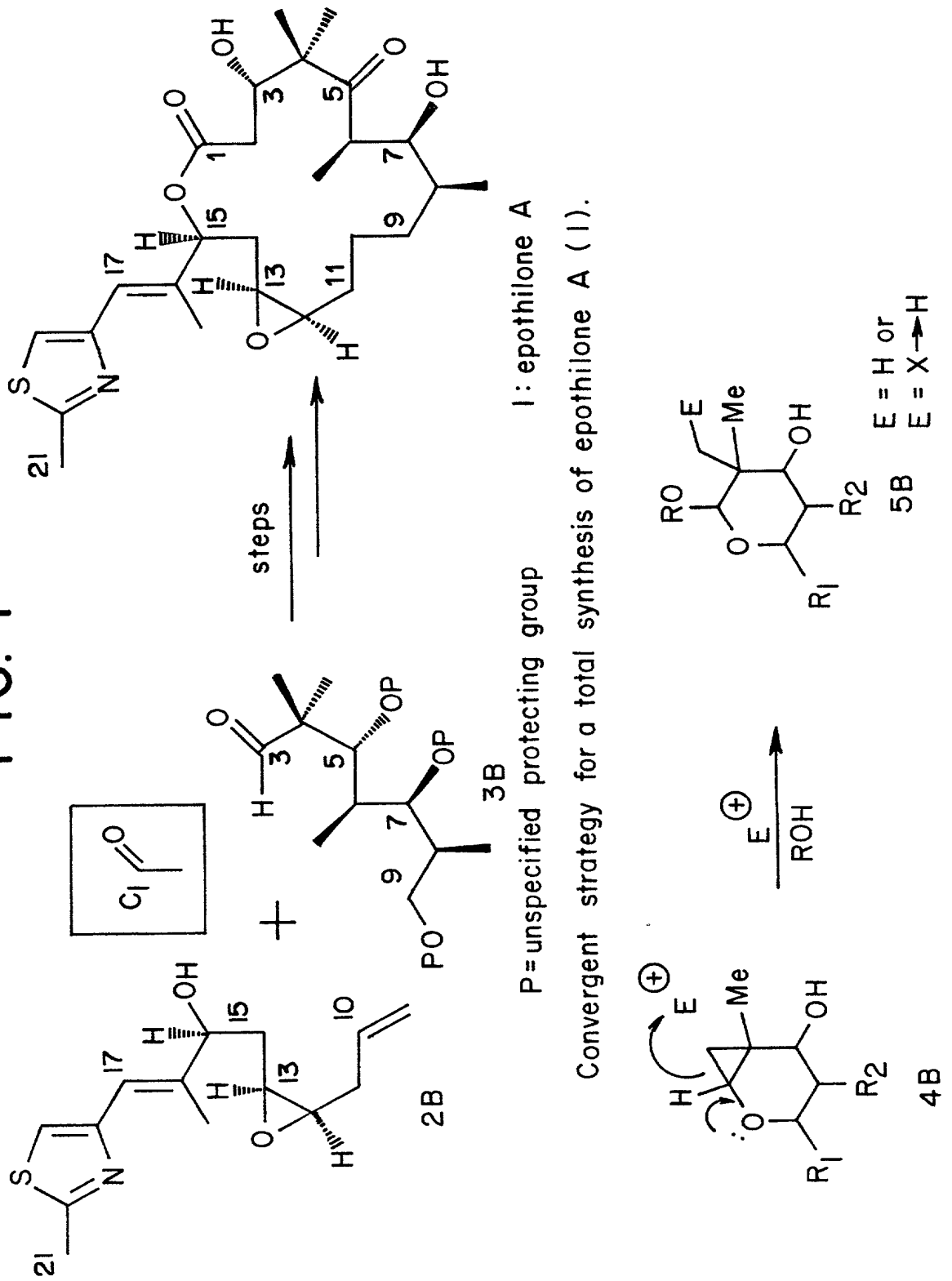


FIG. 8

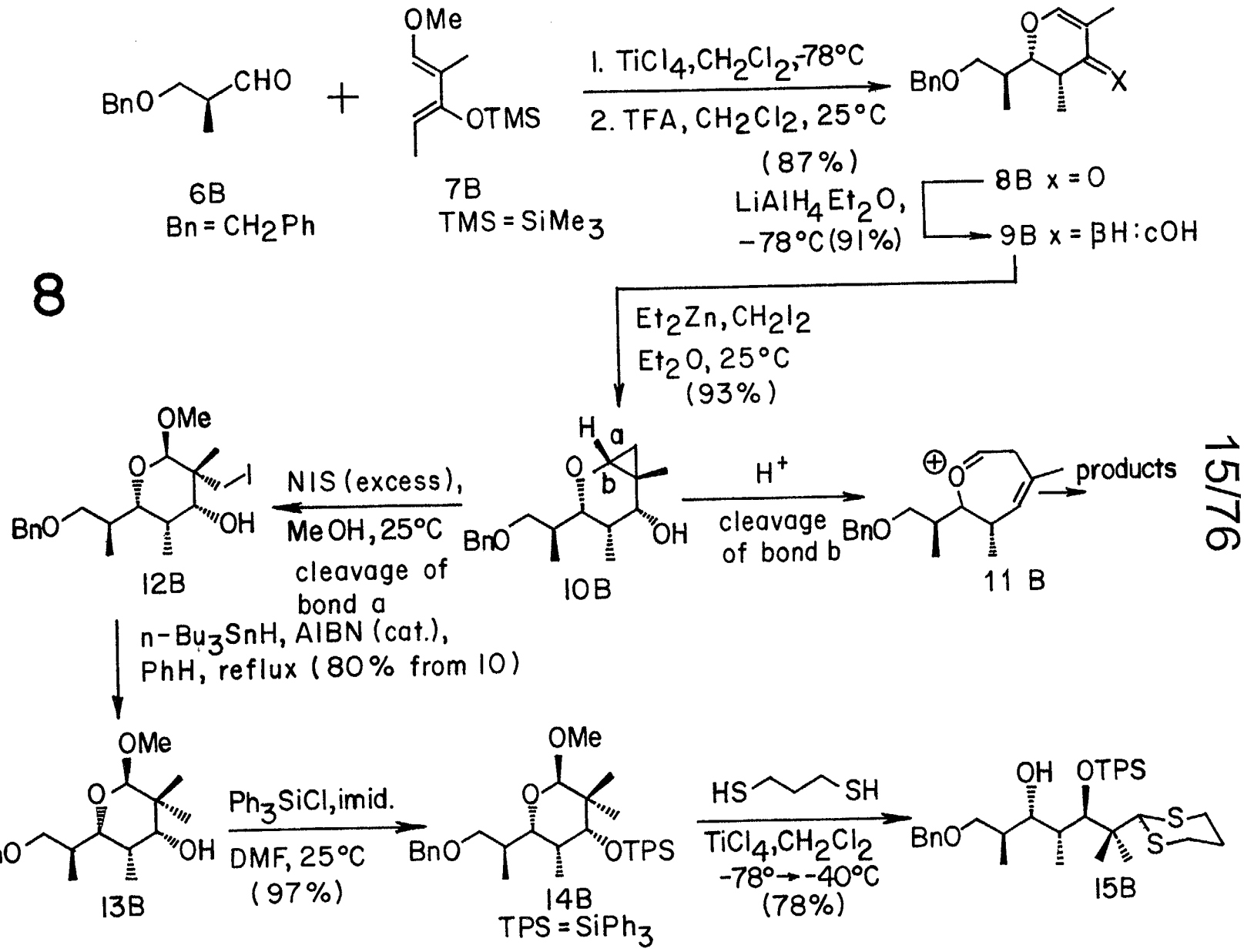

OMe
BnO
CHO
OTMS
6B
Bn = CH2Ph
7B
TMS = SiMe3
1. TiCl4, CH2Cl2, -78°C
2. TFA, CH2Cl2, 25°C
(87%)
X
8B x = O
LiAlH4 Et2O,
-78°C (91%)
9B x = βH:αOH
Et2Zn, CH2I2
Et2O, 25°C
(93%)
H
a
b
I
OH
12B
NIS (excess),
MeOH, 25°C
cleavage of
bond a
10B
H+
cleavage
of bond b
11 B
products
n-Bu3SnH, AIBN (cat.),
PhH, reflux (80% from 10)
13B
Ph3SiCl, imid.
DMF, 25°C
(97%)
OTPS
14B
TPS = SiPh3
HS
SH
TiCl4, CH2Cl2
-78° → -40°C
(78%)
15B

FIG. 9

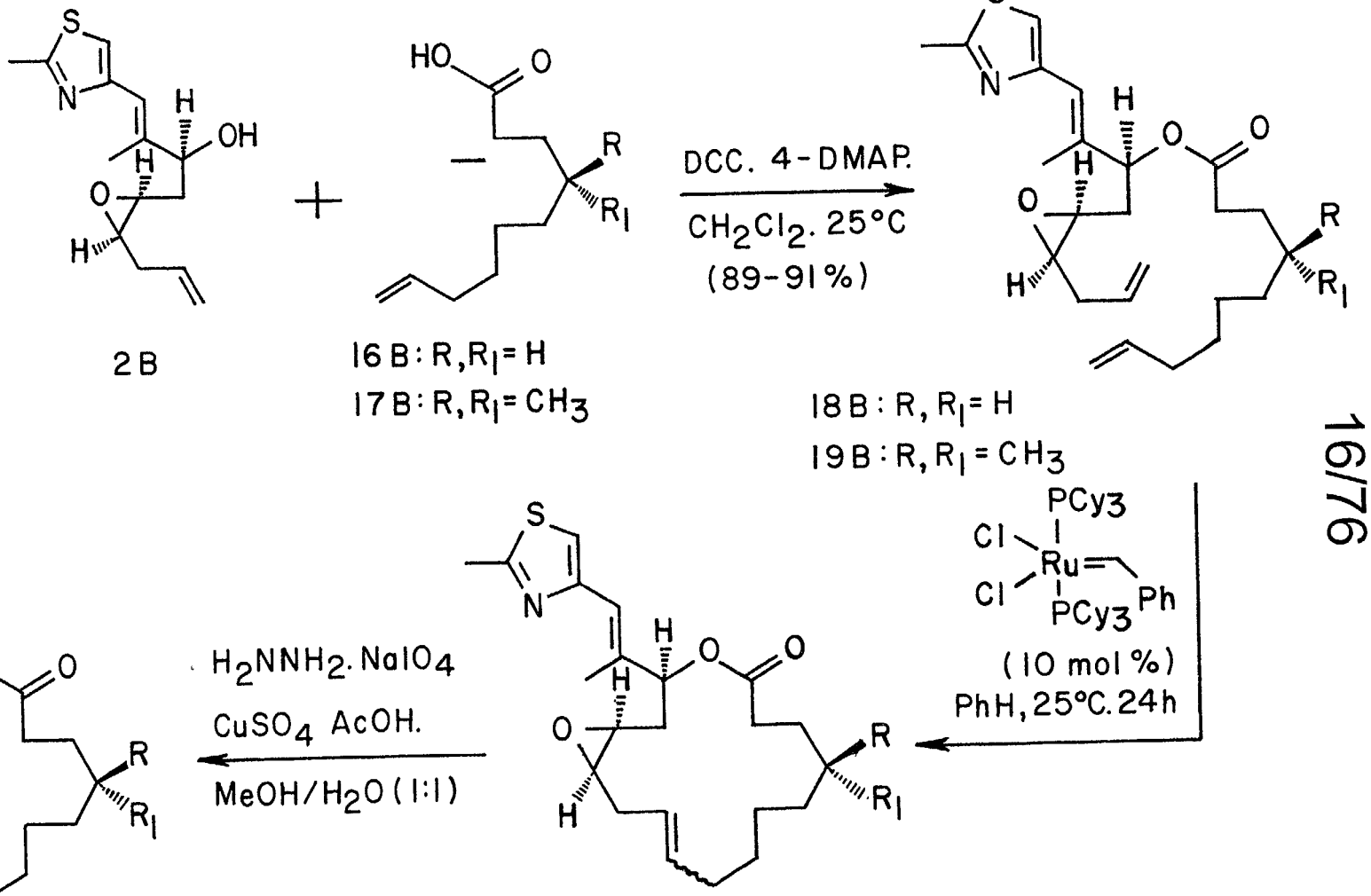

2B
16B: R,R1 = H
17B: R,R1 = CH3
DCC. 4-DMAP.
CH2Cl2. 25°C
(89-91%)
18B: R, R1 = H
19B: R, R1 = CH3
PCy3
Cl
Ru=
Cl
PCy3
Ph
(10 mol %)
PhH, 25°C. 24h
H2NNH2. NaIO4
CuSO4 AcOH.
MeOH/H2O (1:1)
20B: R,R1 = H (E:Z ca. 1:1. 45%)
21B: R,R1 = CH (one stereoisomer. 70%)
22B: R,R1 = H

FIG. 10

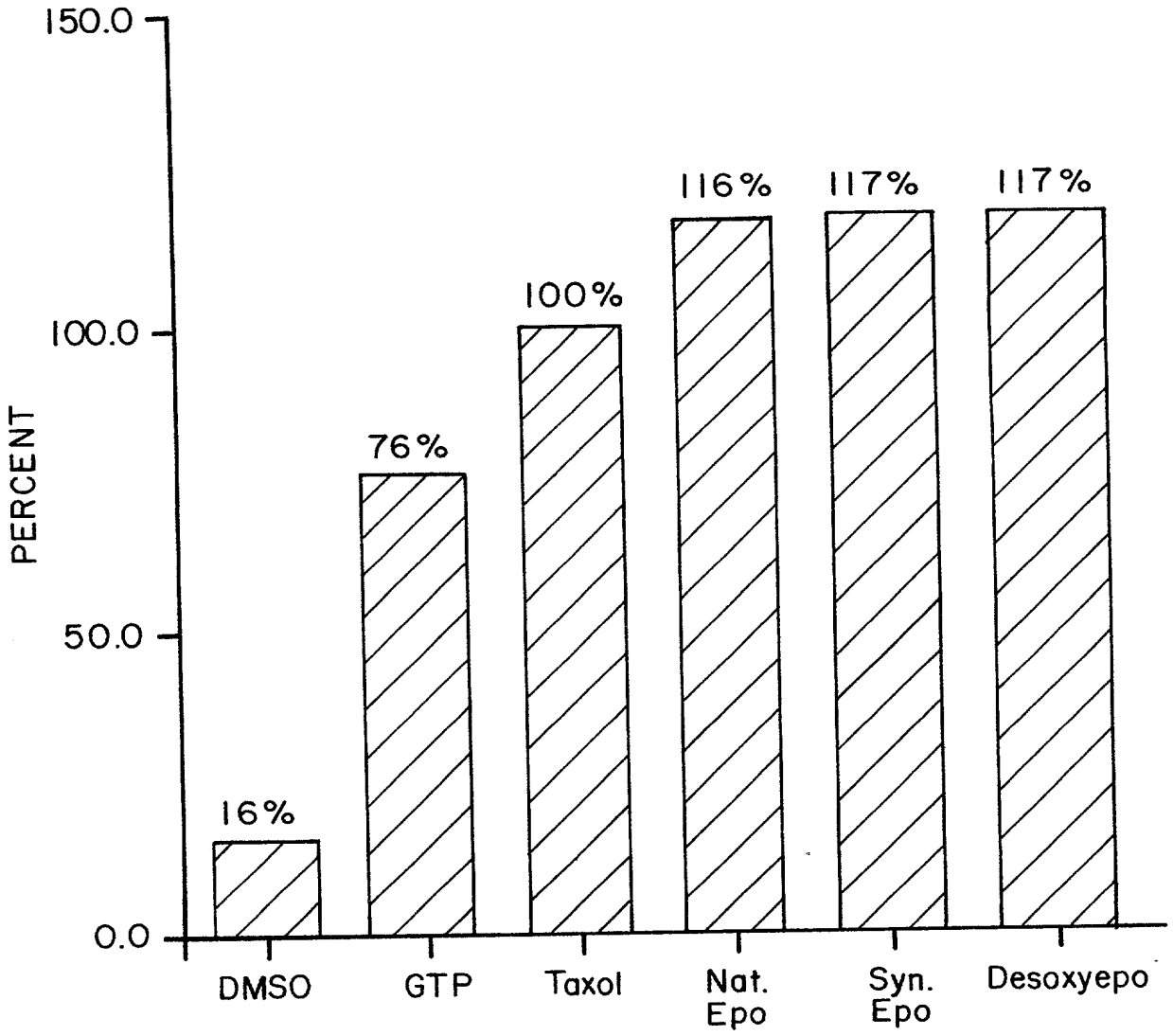
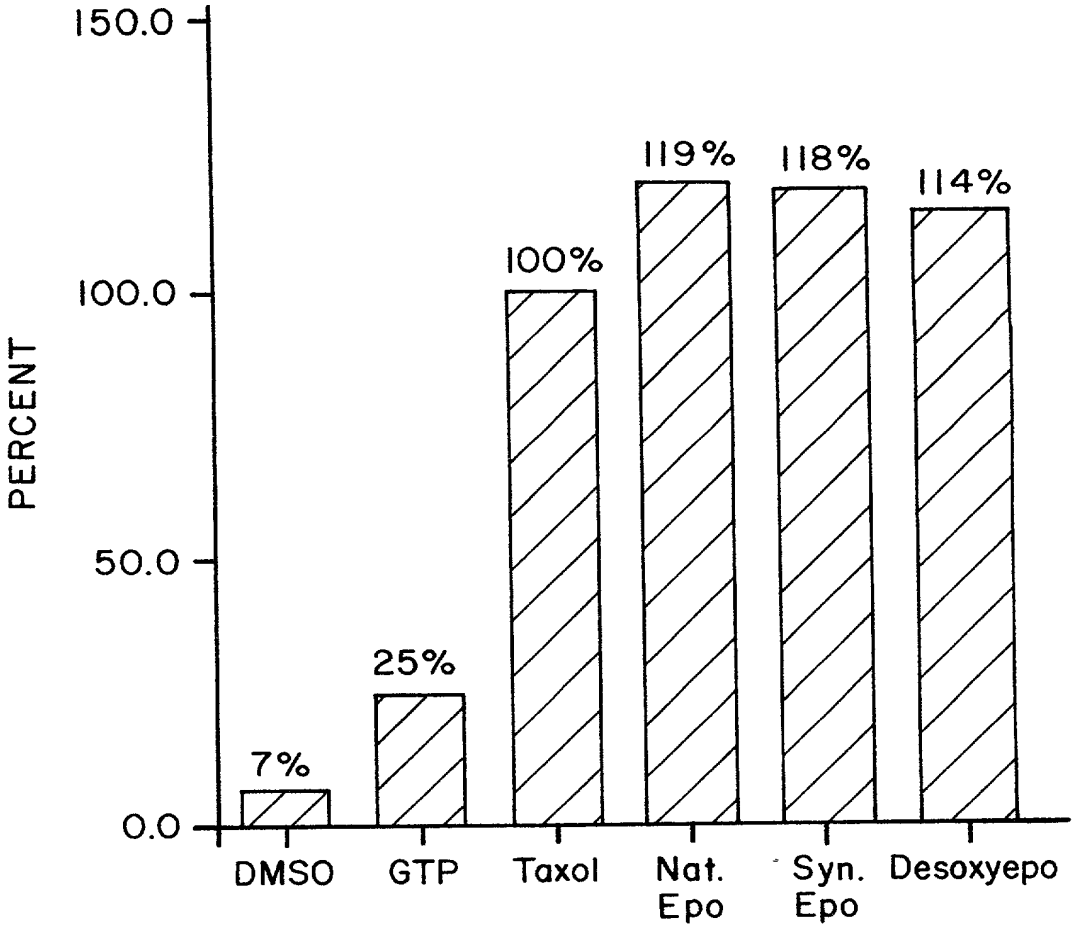

150.0
100.0
50.0
0.0
PERCENT
16%
76%
100%
116%
117%
117%
DMSO
GTP
Taxol
Nat. Epo
Syn. Epo
Desoxyepo

FIG. 11


150.0
100.0
50.0
0.0
PERCENT
7%
25%
100%
119%
118%
114%
DMSO
GTP
Taxol
Nat. Epo
Syn. Epo
Desoxyepo

T0h02F" T25h0001

FIG. 13

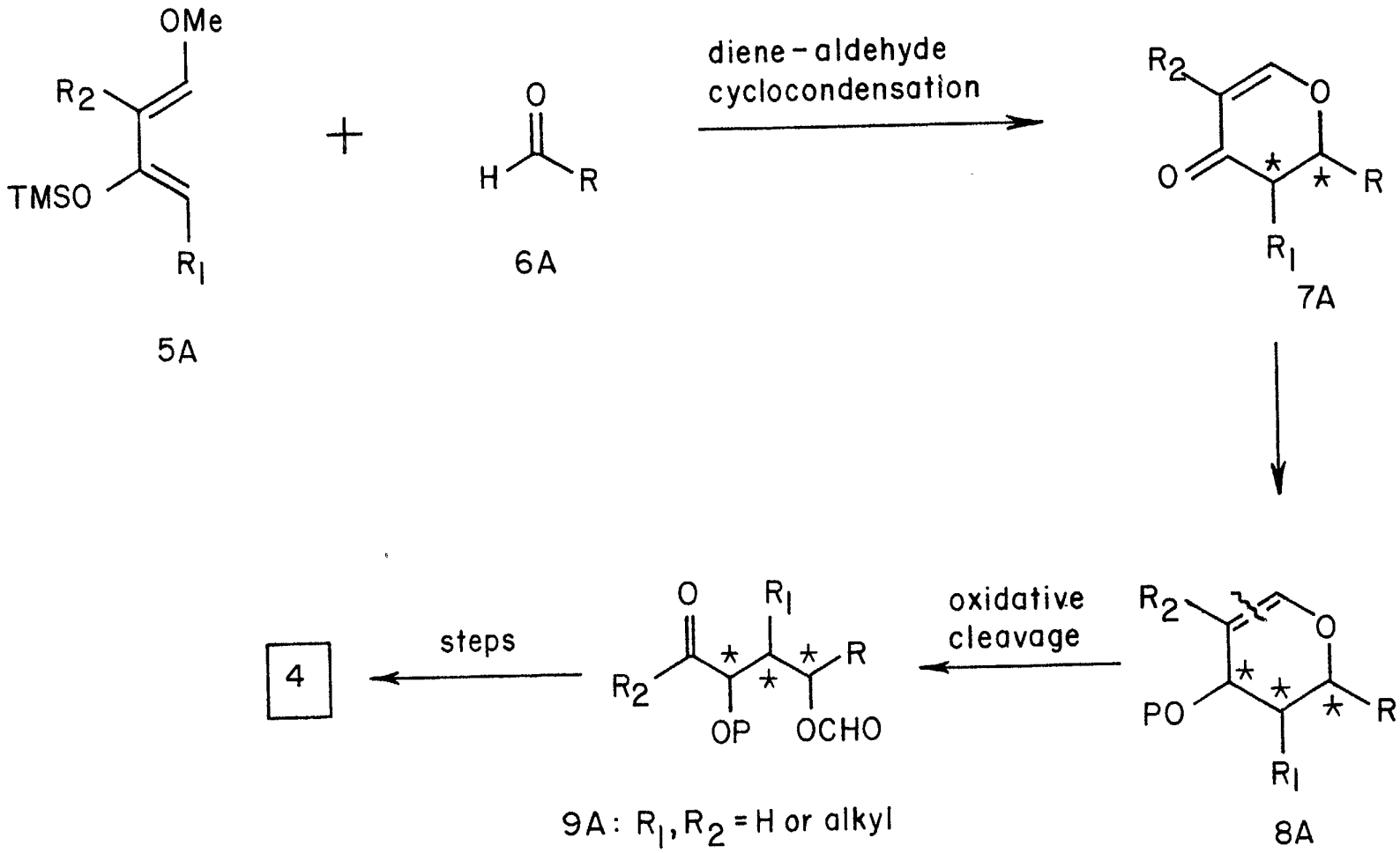


FIG. 14A

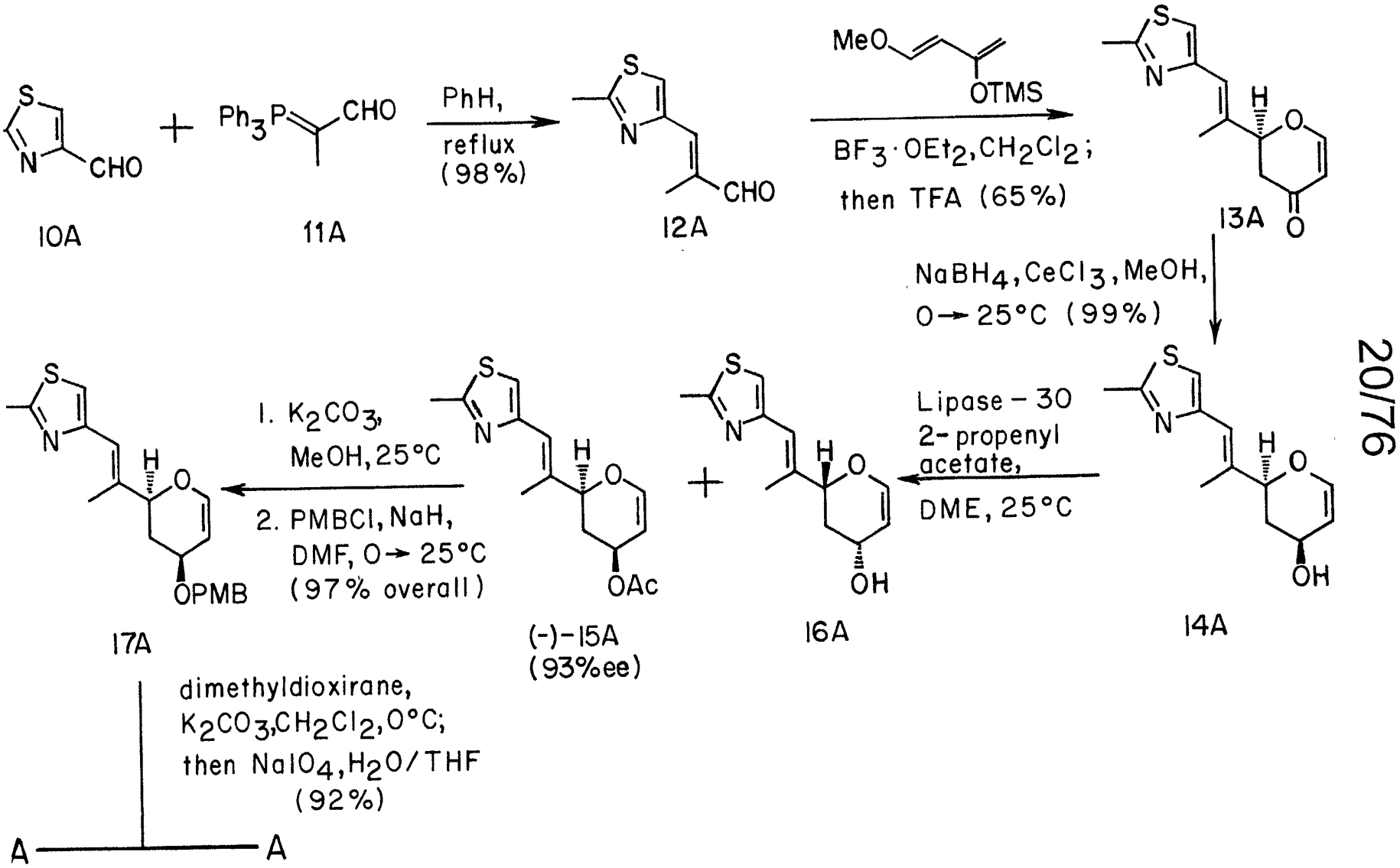

10A
11A
PhH, reflux (98%)
12A
MeO
OTMS
BF3·OEt2, CH2Cl2; then TFA (65%)
13A
NaBH4, CeCl3, MeOH, 0→25°C (99%)
14A
Lipase – 30
2-propenyl acetate,
DME, 25°C
16A
(-)-15A (93%ee)
1. K2CO3, MeOH, 25°C
2. PMBCl, NaH, DMF, 0→25°C (97% overall)
17A
dimethyldioxirane, K2CO3, CH2Cl2, 0°C; then NaIO4, H2O/THF (92%)
A
A

FIG. 14B

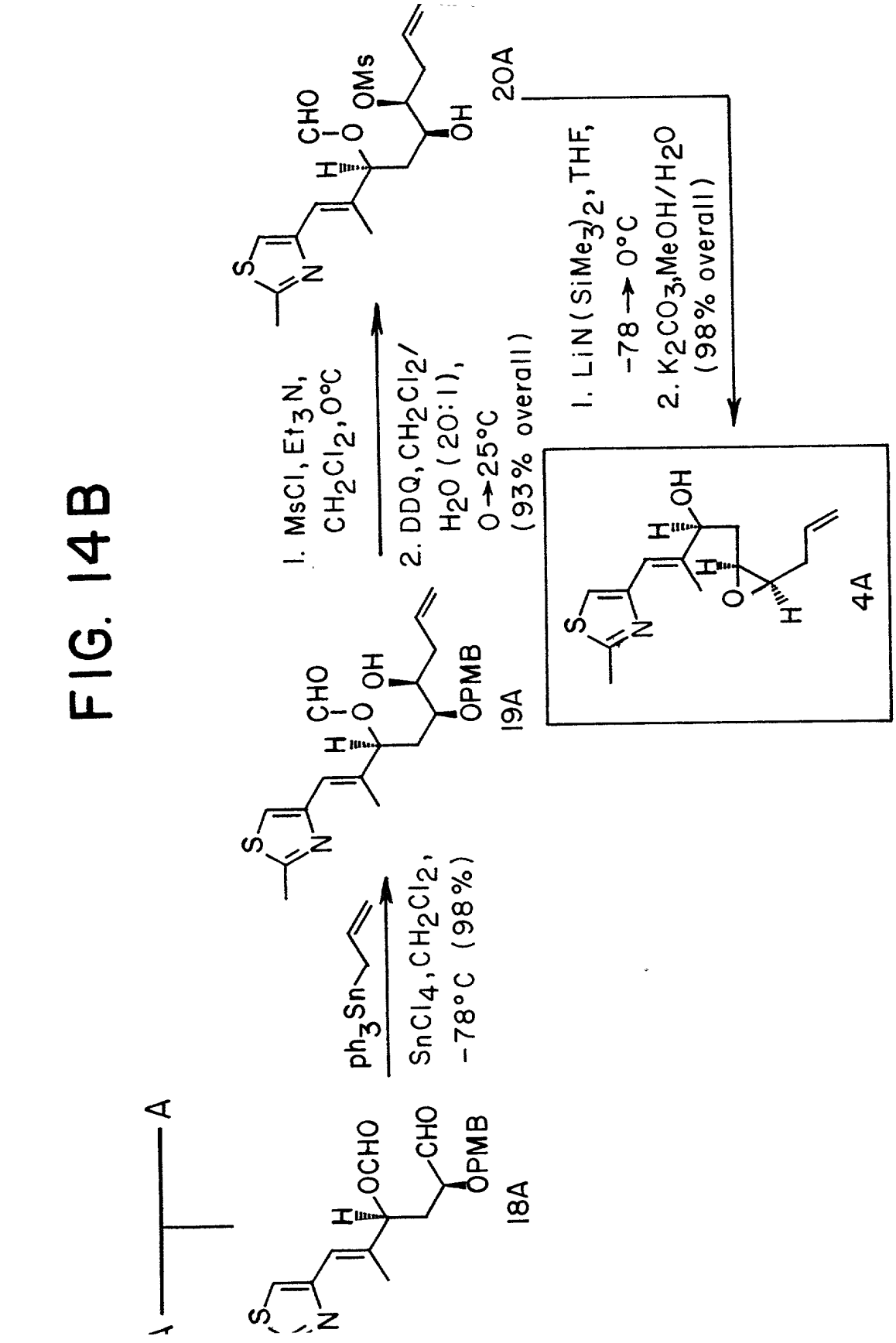
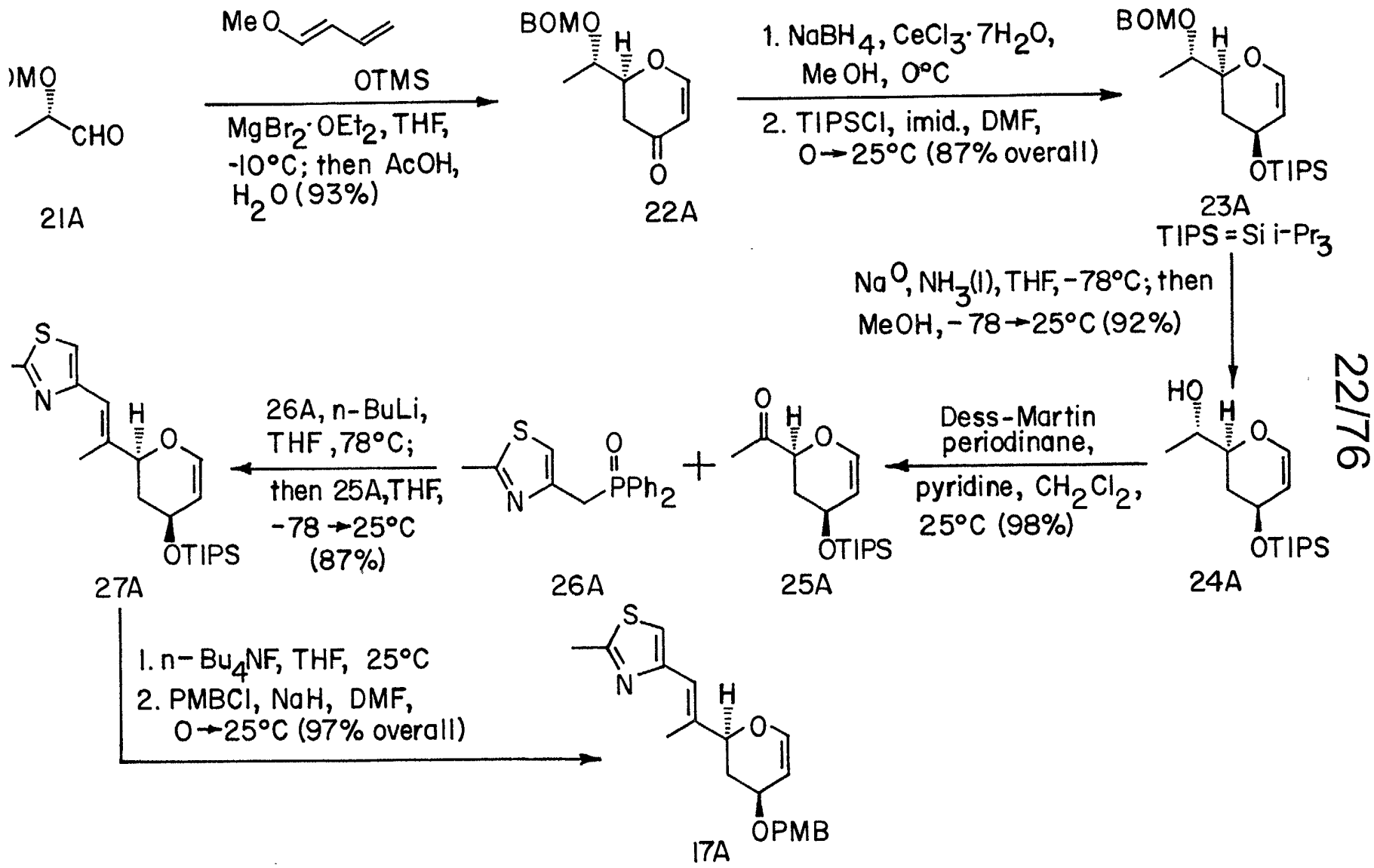
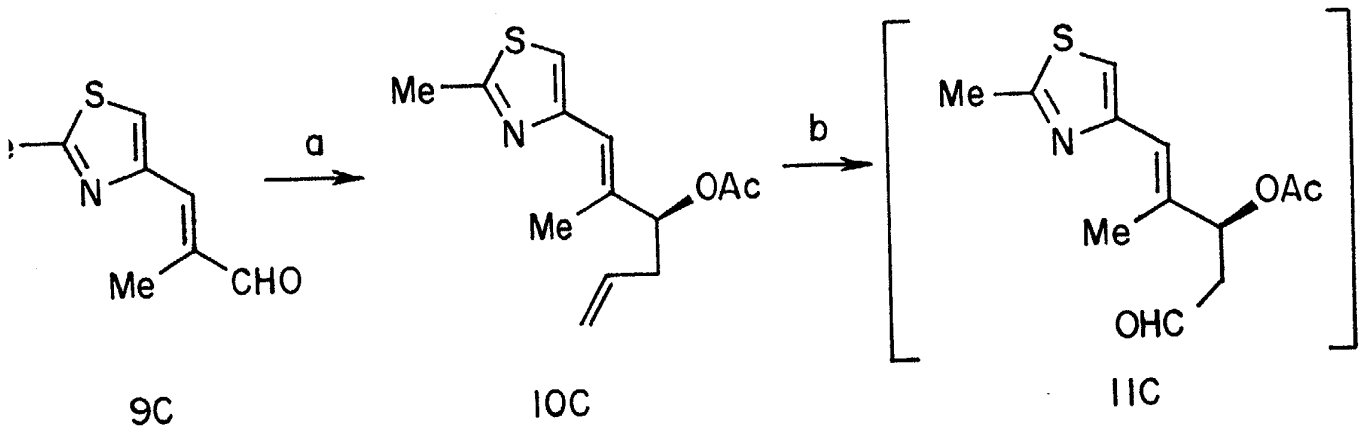

A
18A
Ph_3Sn
$SnCl_4, CH_2Cl_2,$
$-78°C$ (98%)
19A
1. MsCl, Et_3N,
CH_2Cl_2, 0°C
2. DDQ, CH_2Cl_2/
H_2O (20:1),
0→25°C
(93% overall)
20A
1. $LiN(SiMe_3)_2$, THF,
−78→0°C
2. K_2CO_3, MeOH/H_2O
(98% overall)
4A

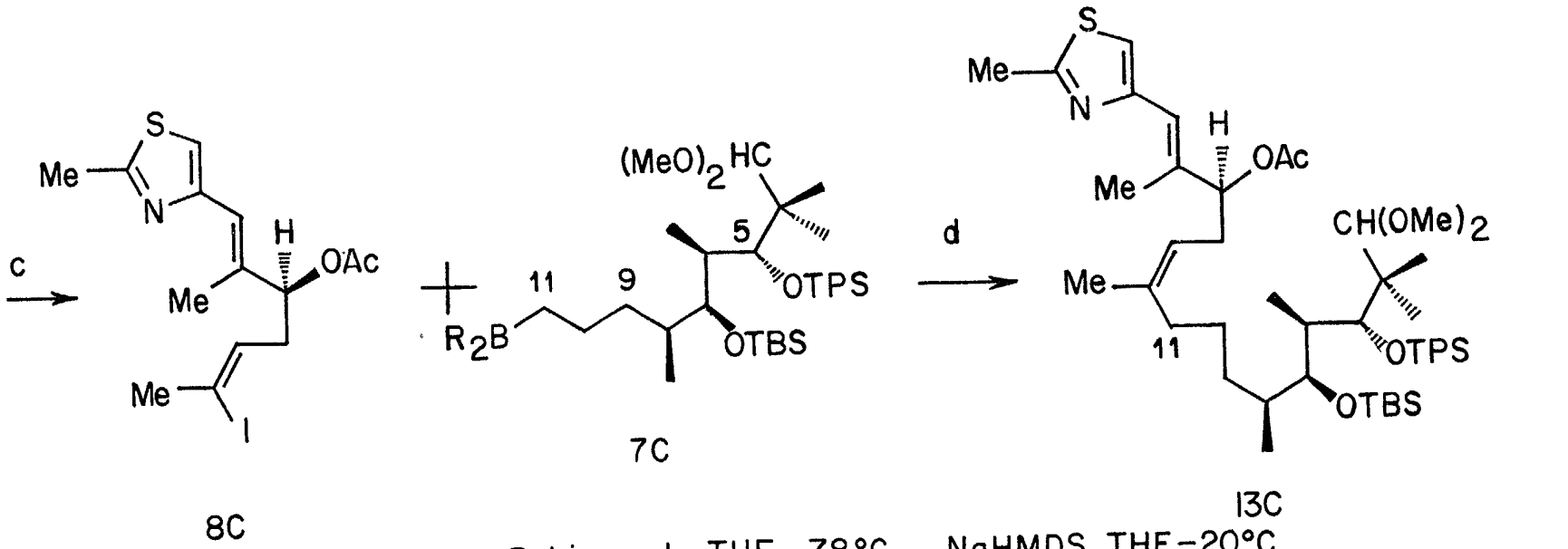
FIG. 15


21A
MeO
OTMS
MgBr2·OEt2, THF,
-10°C; then AcOH,
H2O (93%)
22A
1. NaBH4, CeCl3·7H2O,
MeOH, 0°C
2. TIPSCl, imid., DMF,
0→25°C (87% overall)
23A
TIPS = Si i-Pr3
Na°, NH3(l), THF, -78°C; then
MeOH, -78→25°C (92%)
24A
Dess-Martin
periodinane,
pyridine, CH2Cl2,
25°C (98%)
25A
26A
26A, n-BuLi,
THF, 78°C;
then 25A, THF,
-78→25°C
(87%)
27A
1. n-Bu4NF, THF, 25°C
2. PMBCl, NaH, DMF,
0→25°C (97% overall)
17A
OPMB



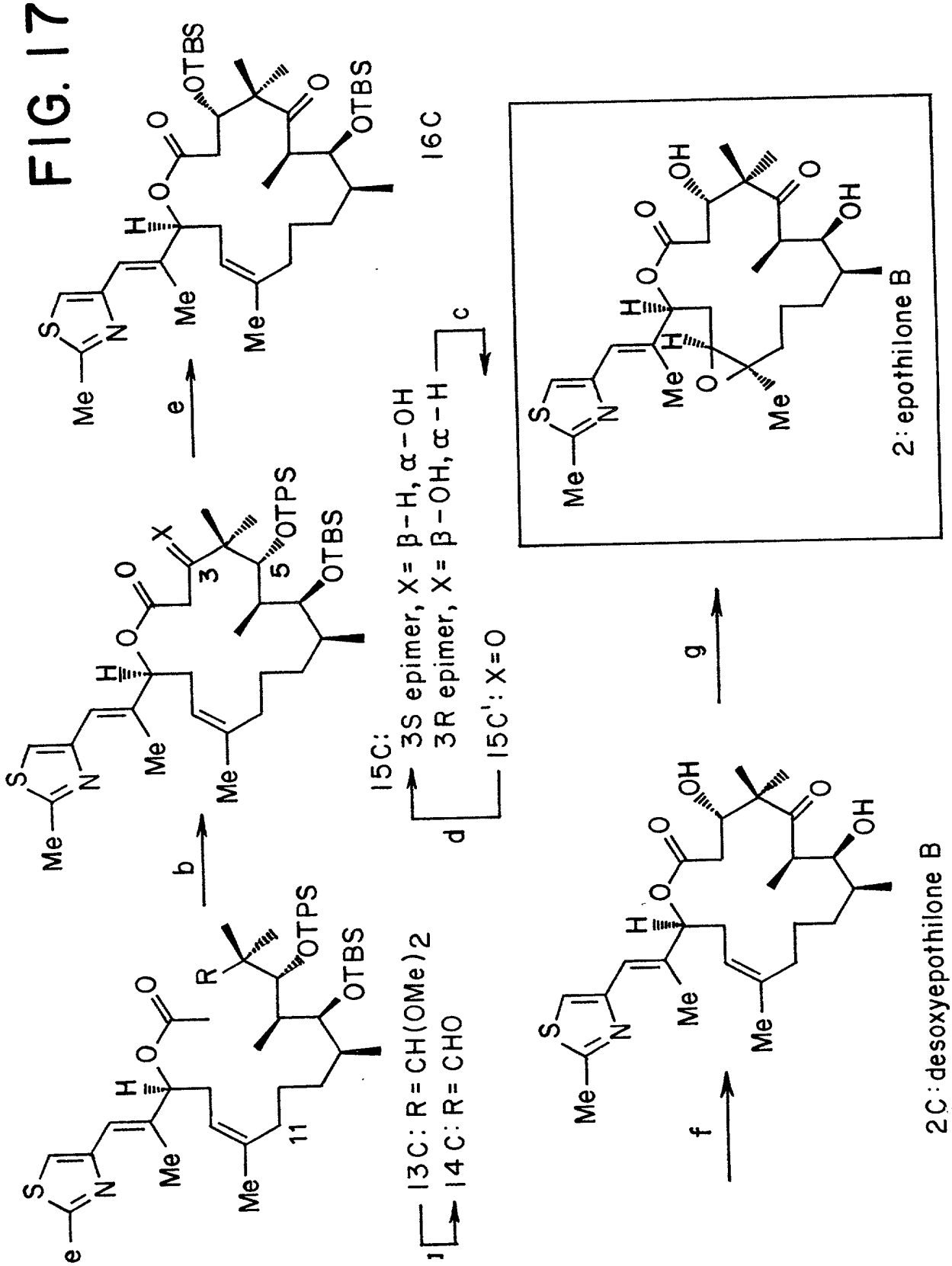
9C 10C 11C

FIG. 16



8C 7C 13C 12C

FIG. 17


16C
15C:
3S epimer, X= β-H, α-OH
3R epimer, X= β-OH, α-H
15C': X=O
13C: R=CH(OMe)2
14C: R=CHO
2: epothilone B
2C: desoxyepothilone B
a
b
c
d
e
f
g

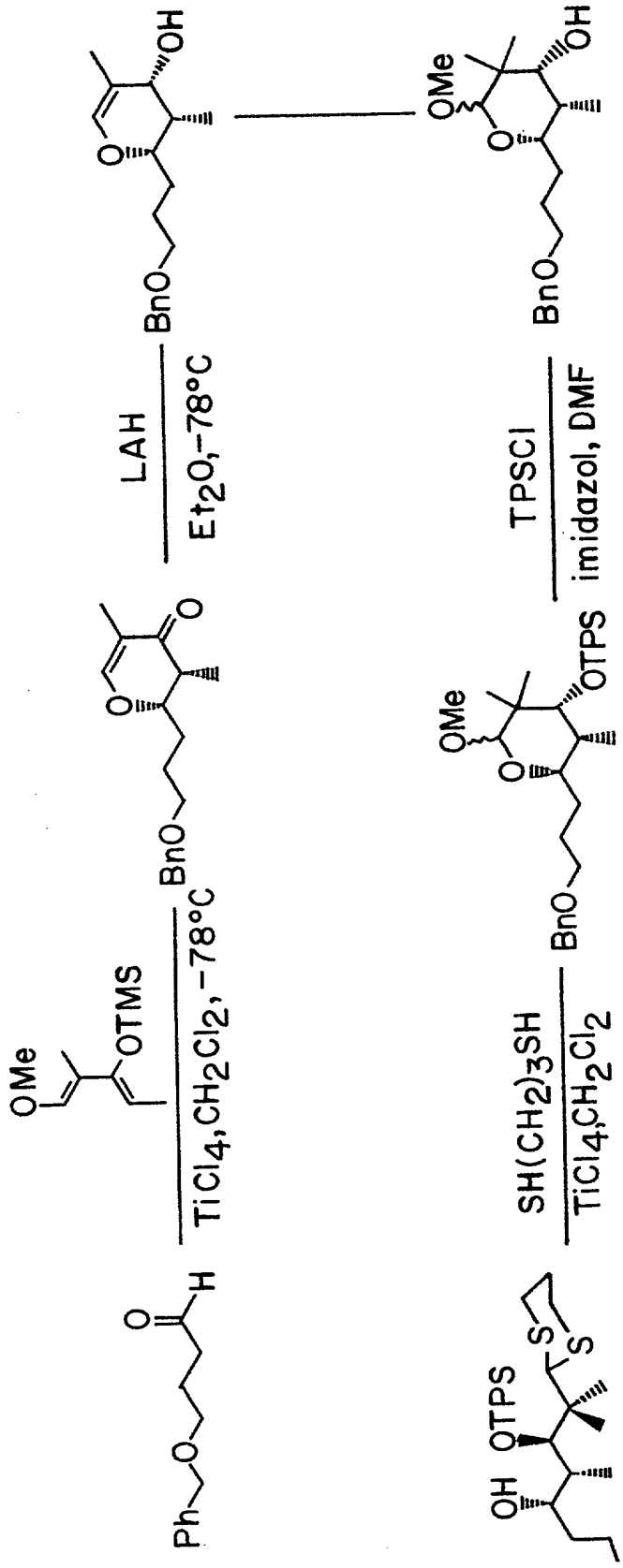

OMe
OTMS
TiCl4, CH2Cl2, −78°C
BnO
LAH
Et2O, −78°C
OH
TPSCl
imidazol, DMF
OTPS
SH(CH2)3SH
TiCl4, CH2Cl2
1. TBSOTf
2. DDQ
3. Wittig olefination
A

FIG. 18A

FIG. 18B

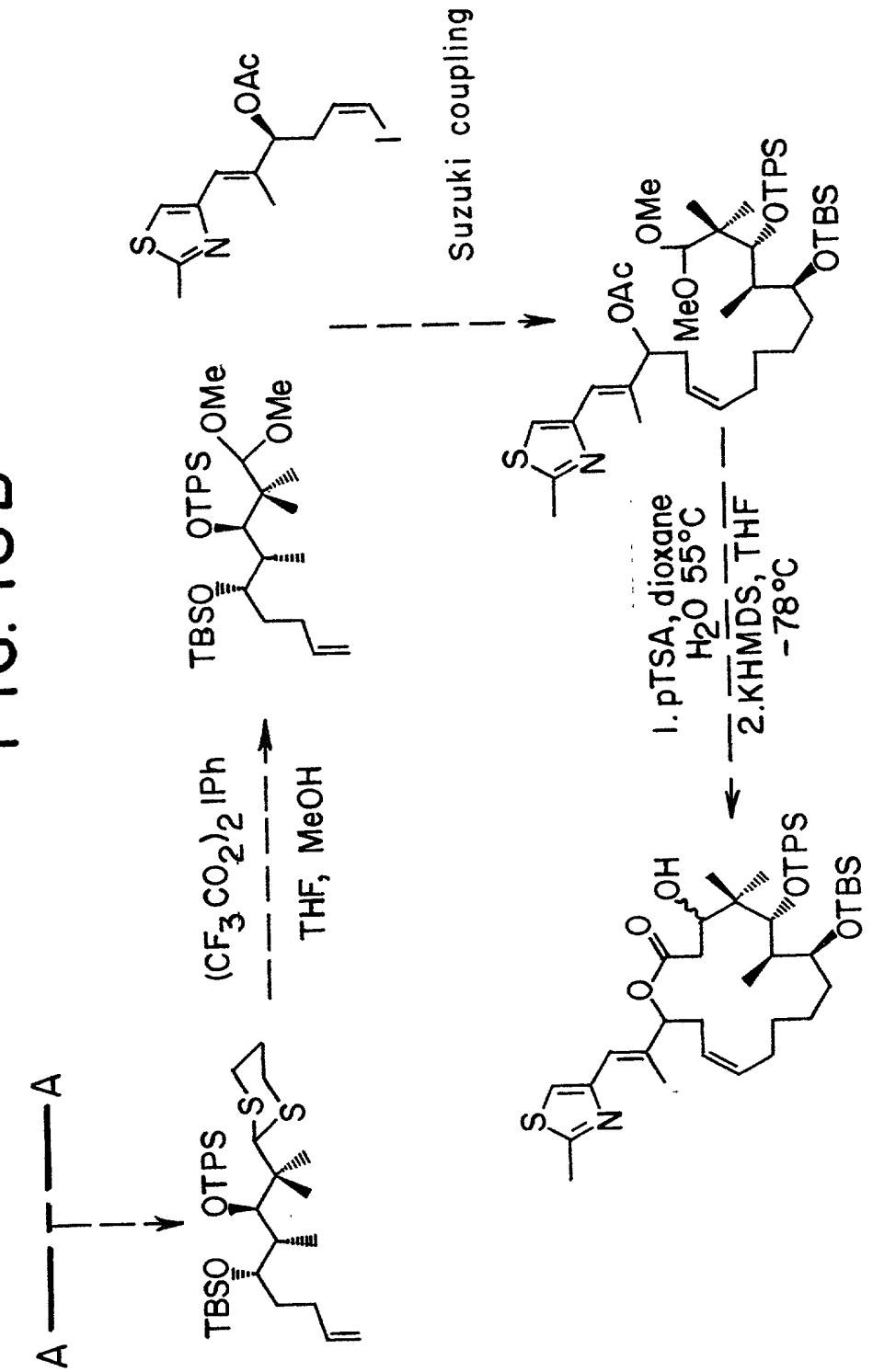

A
A
TBSO
OTPS
S
S
(CF3CO2)2IPh
THF, MeOH
TBSO
OTPS
OMe
OMe
Suzuki coupling
OAc
I
S
N
1. pTSA, dioxane
H2O 55°C
2. KHMDS, THF
-78°C
OAc
OMe
MeO
OTPS
OTBS
S
N
OH
O
O
OTPS
OTBS
S
N

FIG. 19A

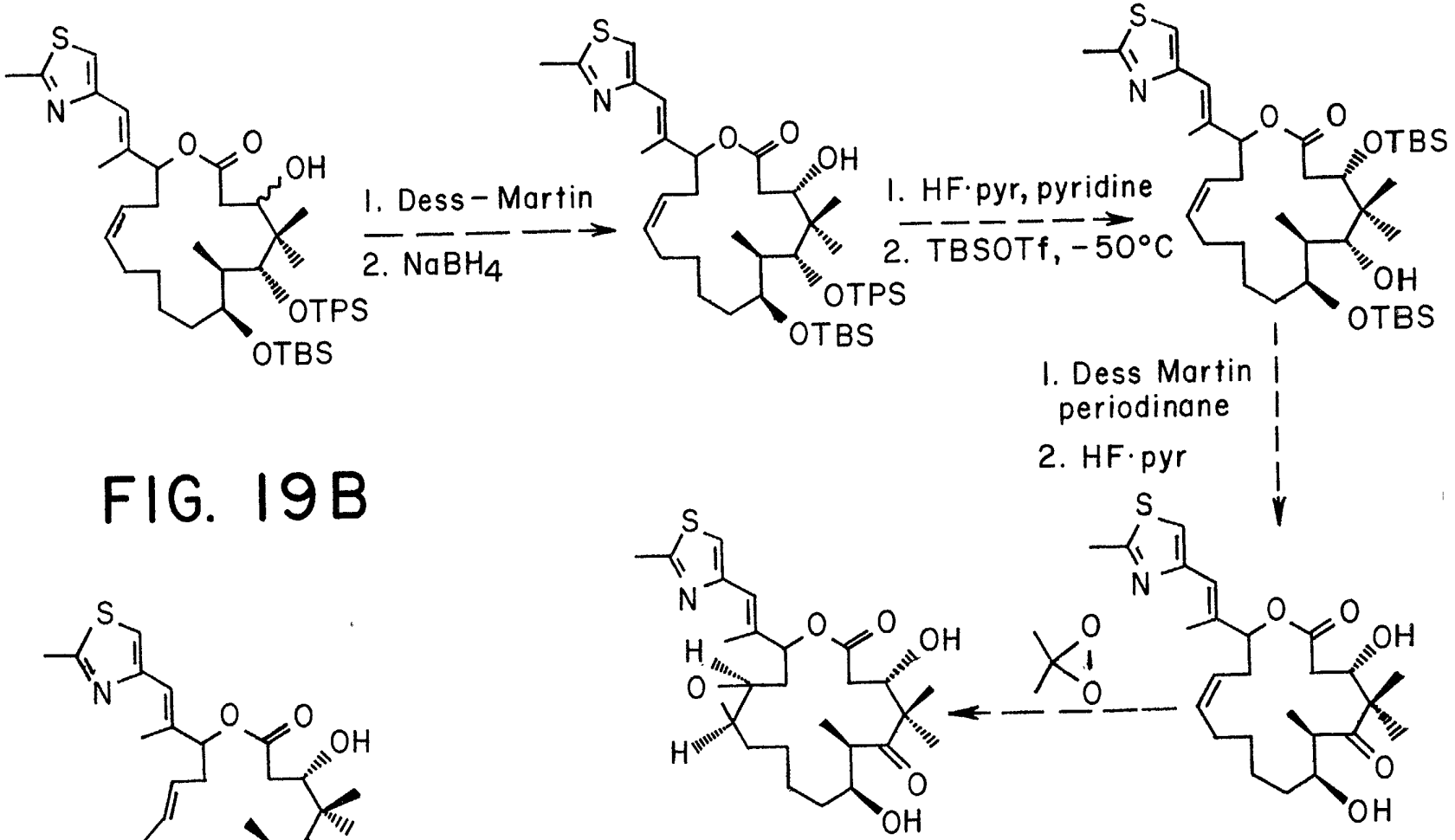


FIG. 19B

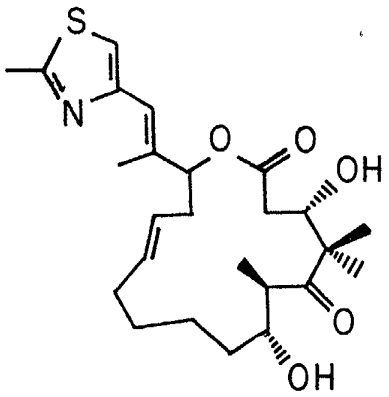
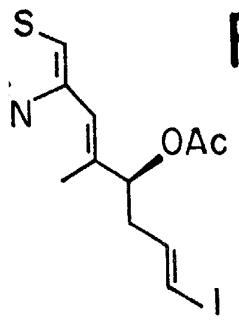


FIG. 19C



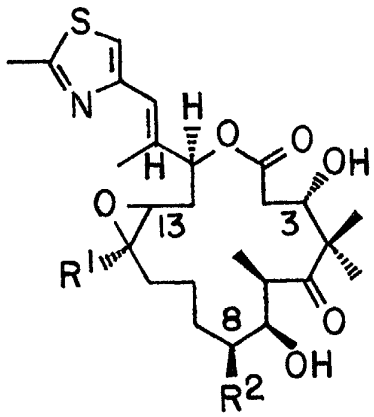


FIG. 20A

$R^1 = H, R^2 = Me$; epothilone A

$R^1 = R^2 = Me$; epothilone B

$R^1 = R^2 = H$; C_8-desmethyl-epothilone A (3D)

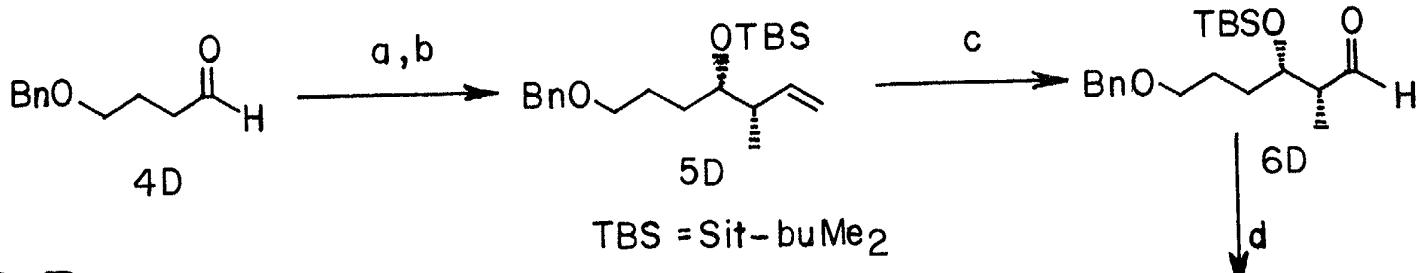


FIG. 20B

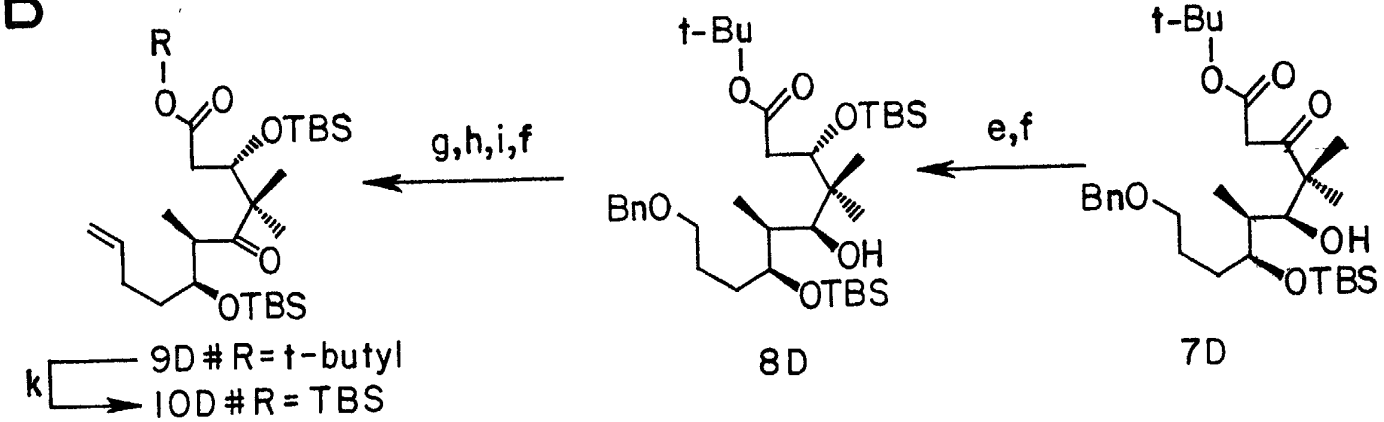


FIG. 21

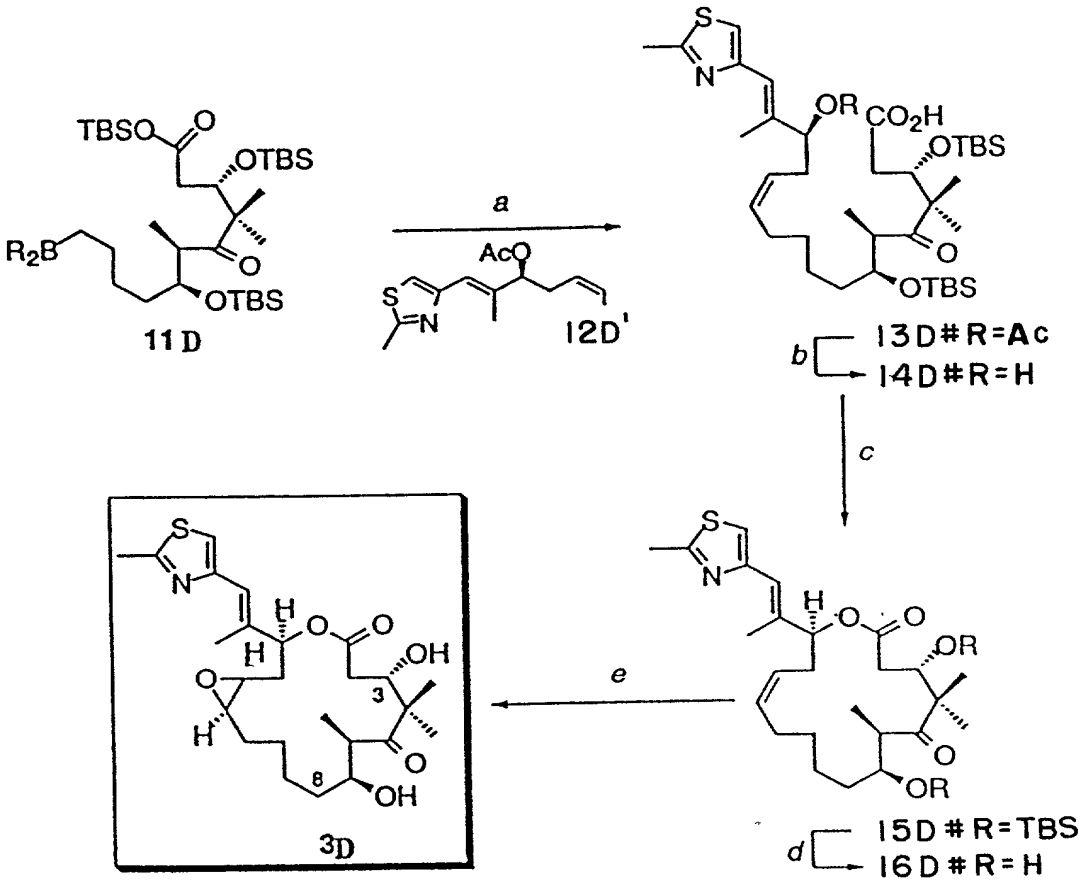

TBSO
OTBS
R2B
OTBS
11D
a
AcO
12D'
OR
CO2H
OTBS
OTBS
13D # R=Ac
b
14D # R=H
c
OR
OR
15D # R=TBS
d
16D # R=H
e
OH
OH
3D

FIG. 22 A

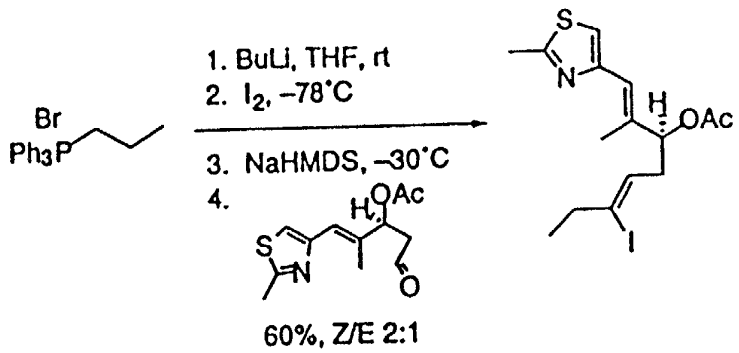


FIG. 22 B

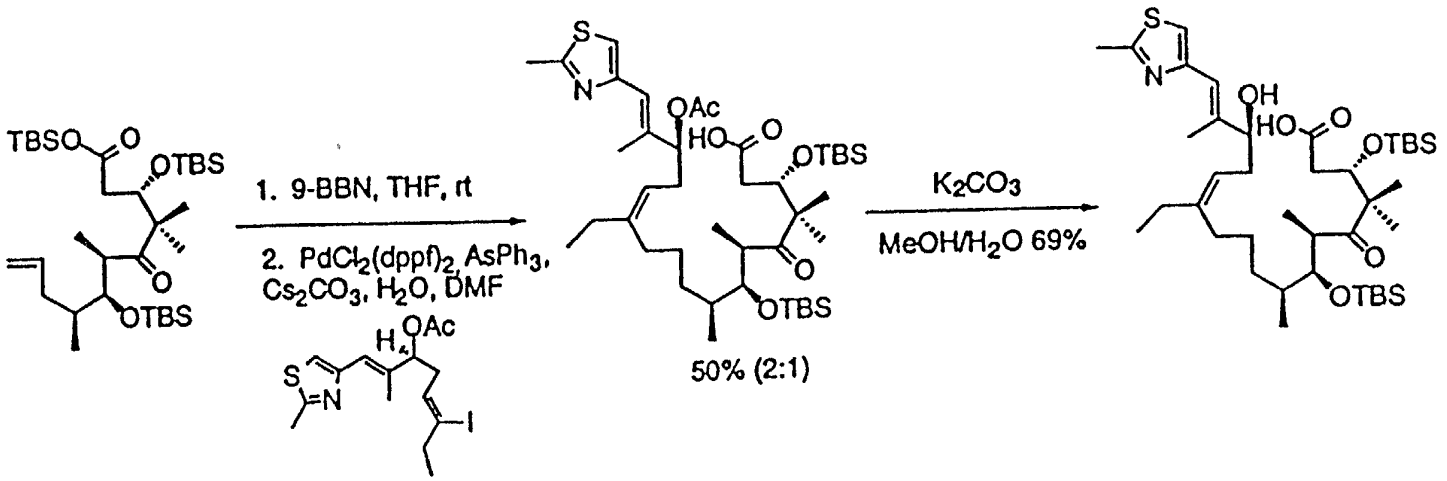


FIG. 22C

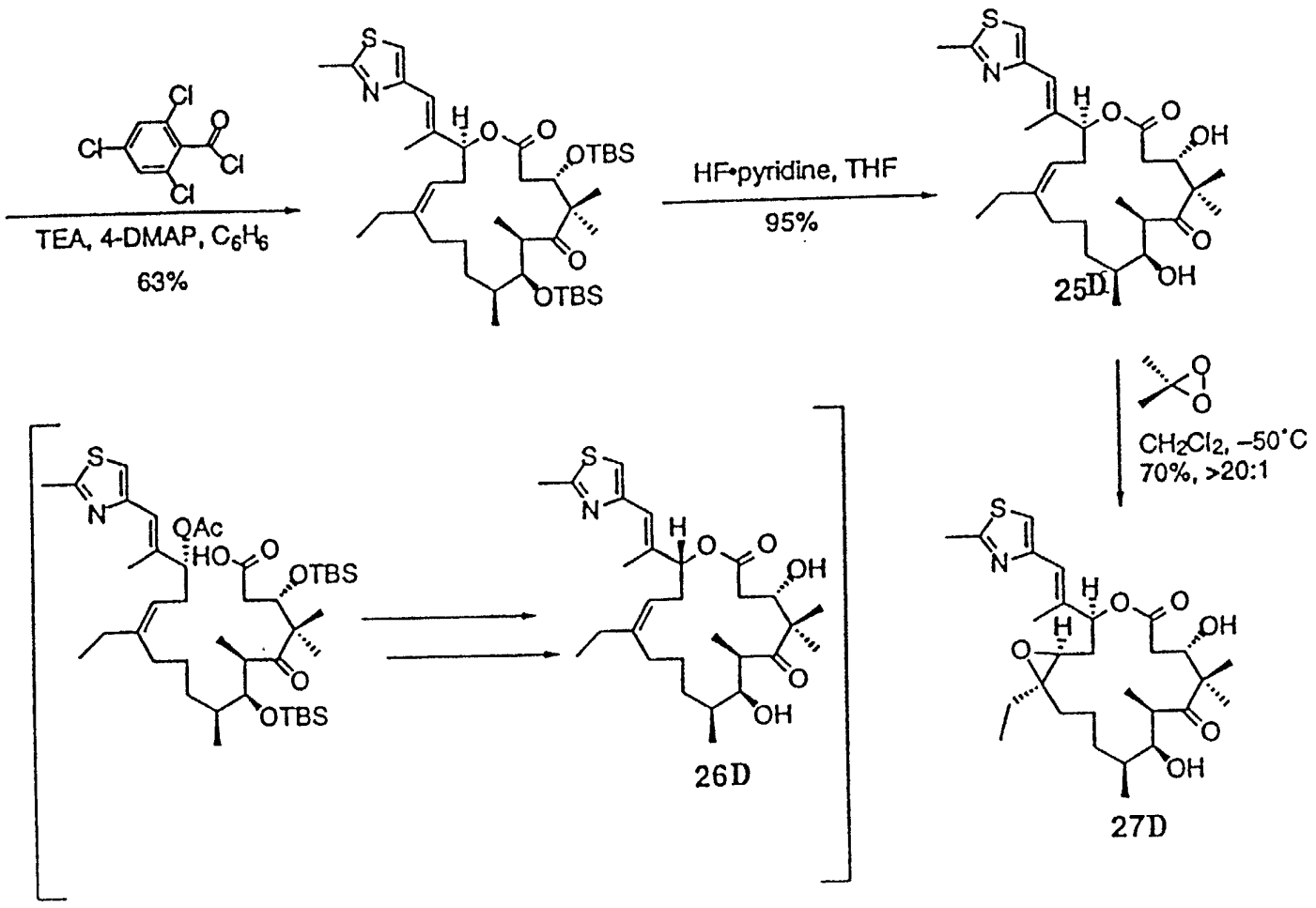

TEA, 4-DMAP, C_6H_6
63%
HF•pyridine, THF
95%
25D
CH_2Cl_2, –50°C
70%, >20:1
26D
27D

FIG. 23A

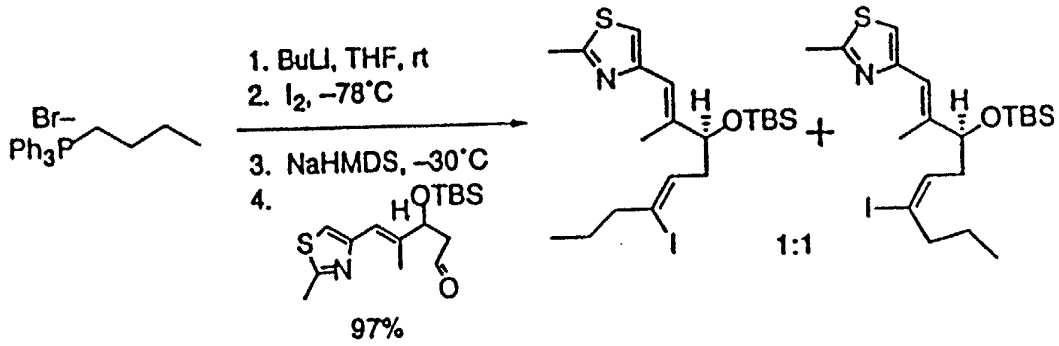
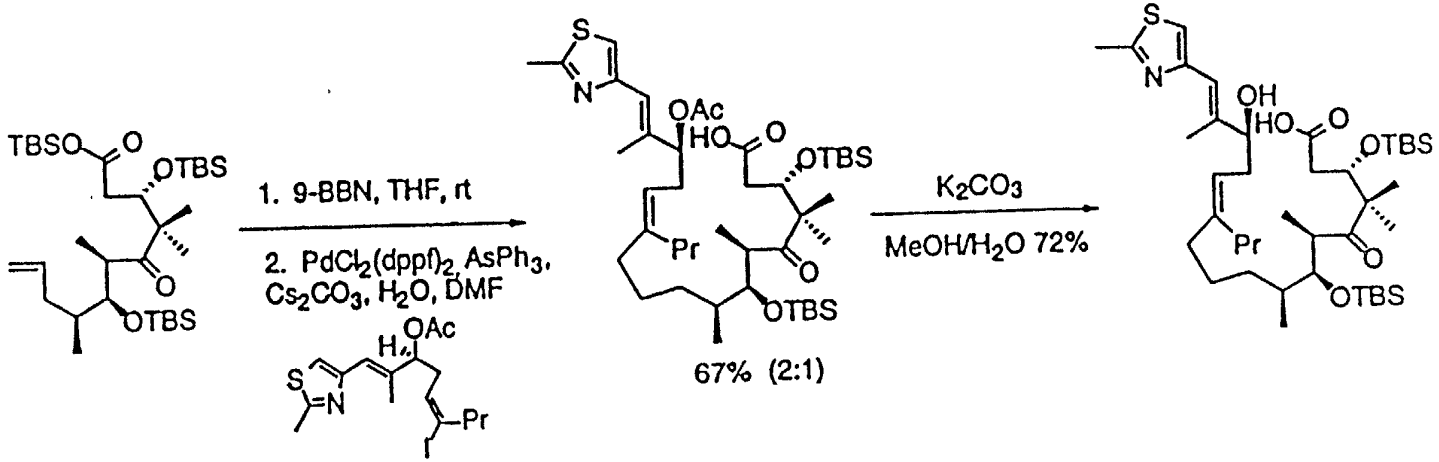


FIG. 23B



Patent Application

FIG. 23C

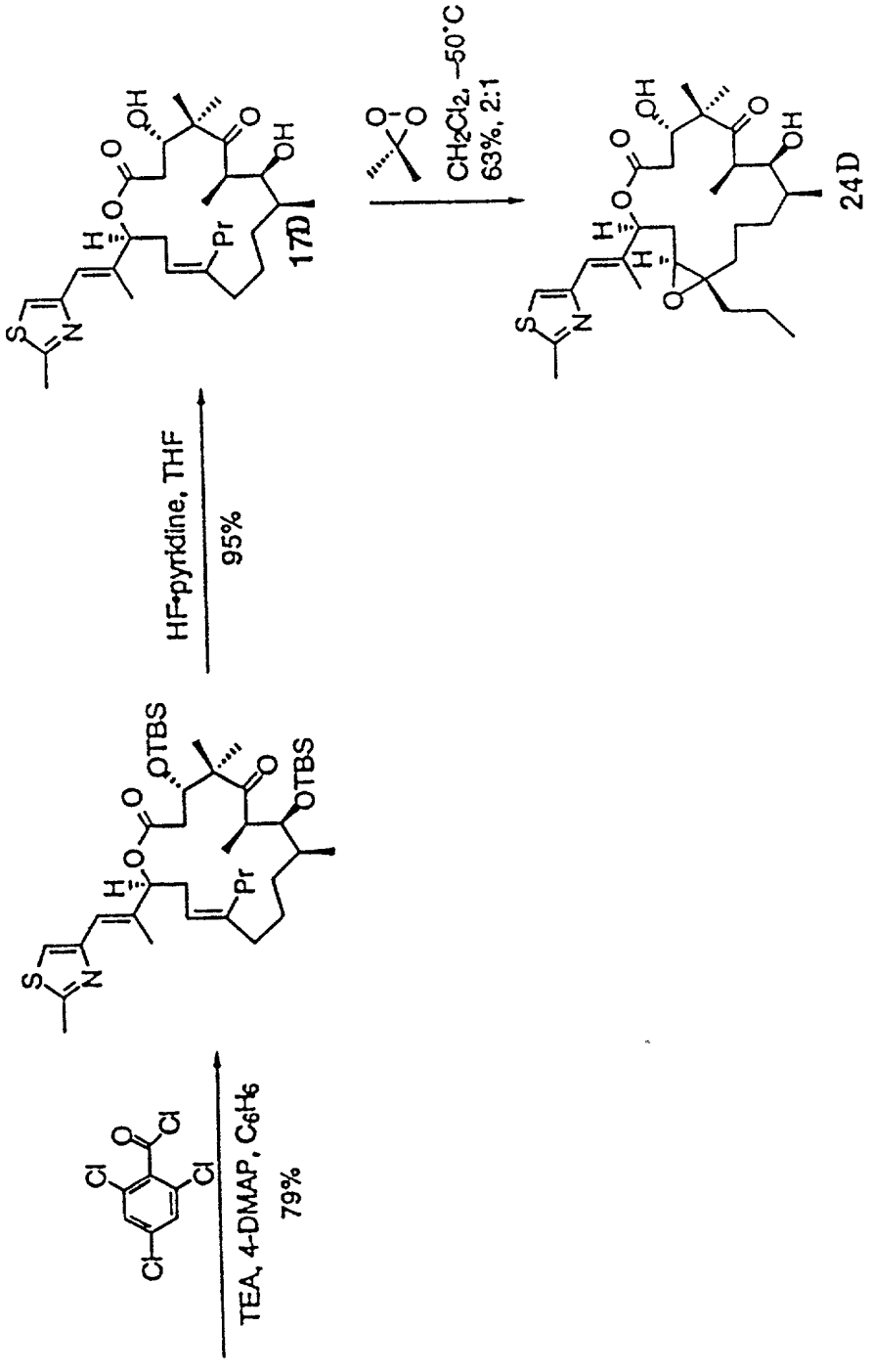


FIG. 24A

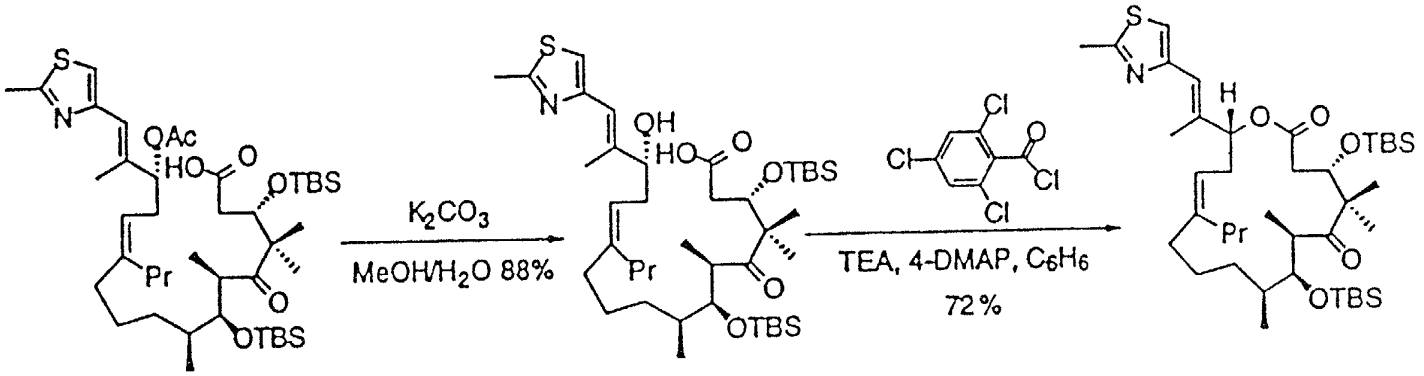


FIG. 24B

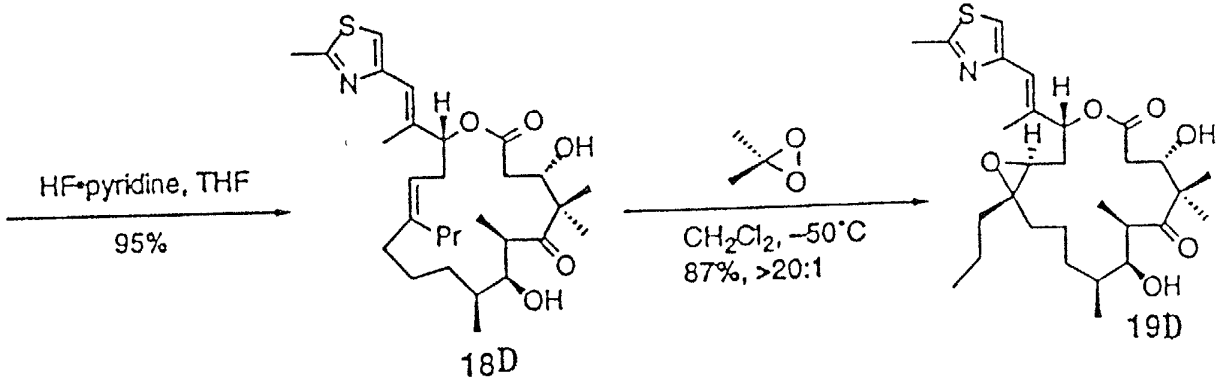


FIG. 25A

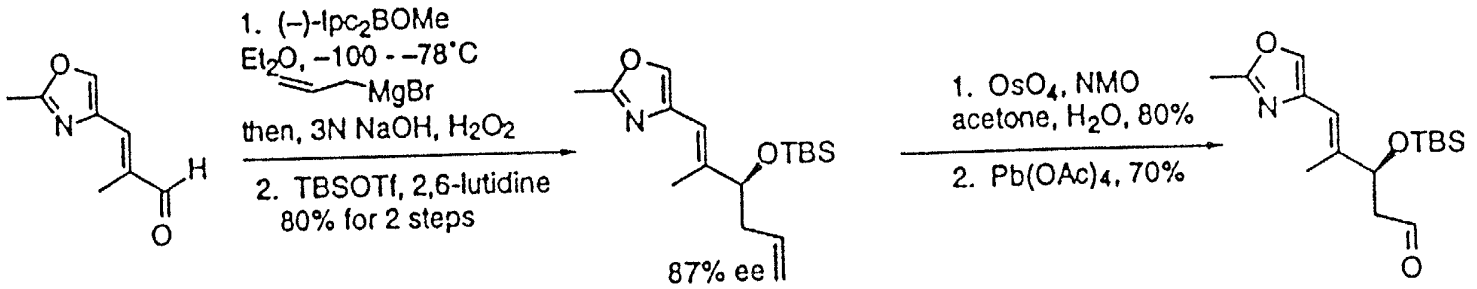


FIG. 25B

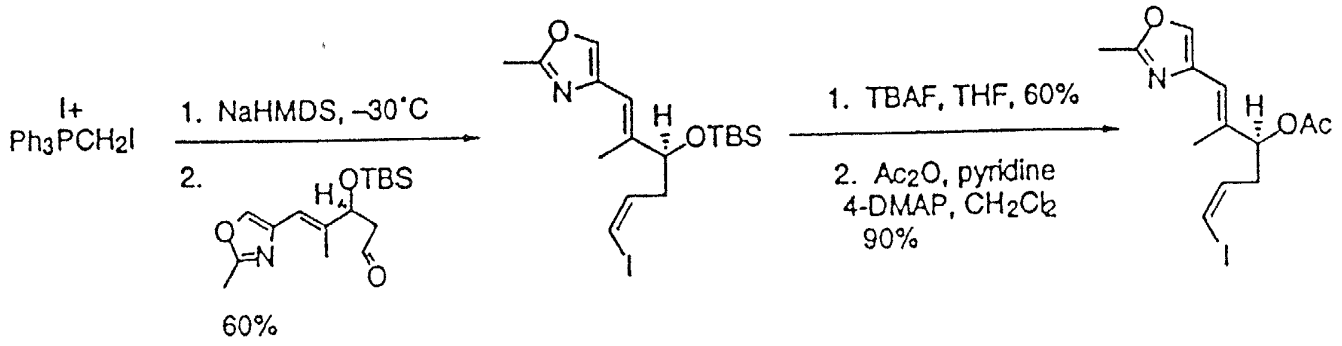


FIG. 25C

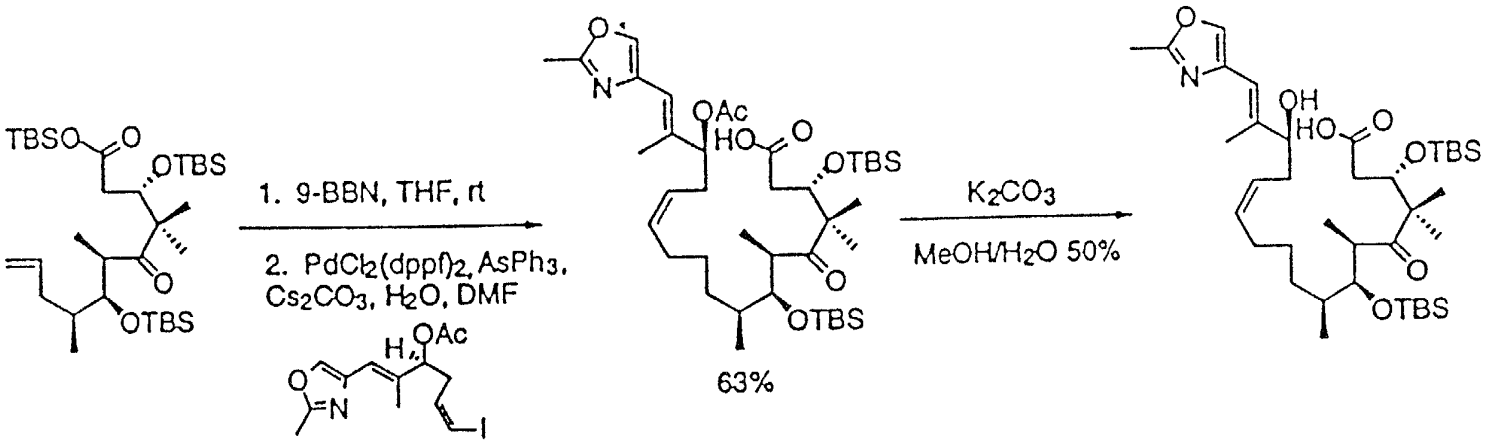
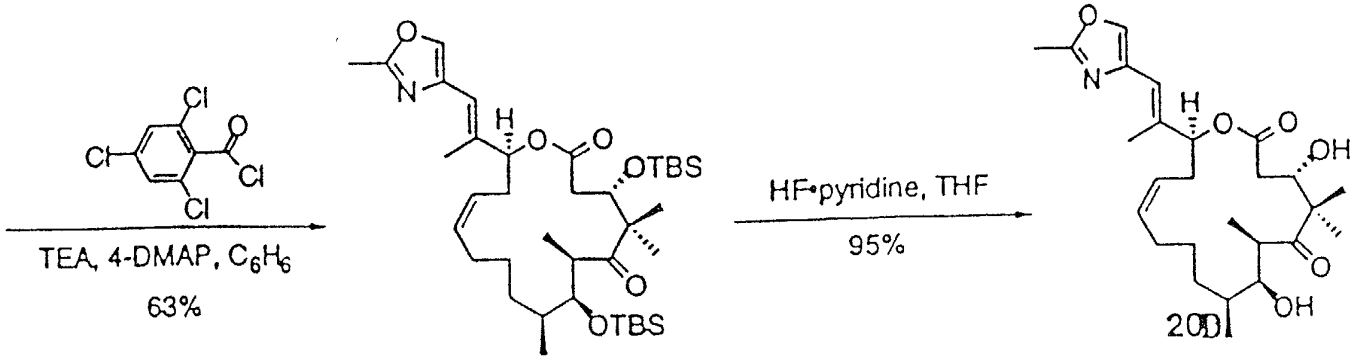


FIG. 25D



T0h02F" T25h000T

FIG. 26A

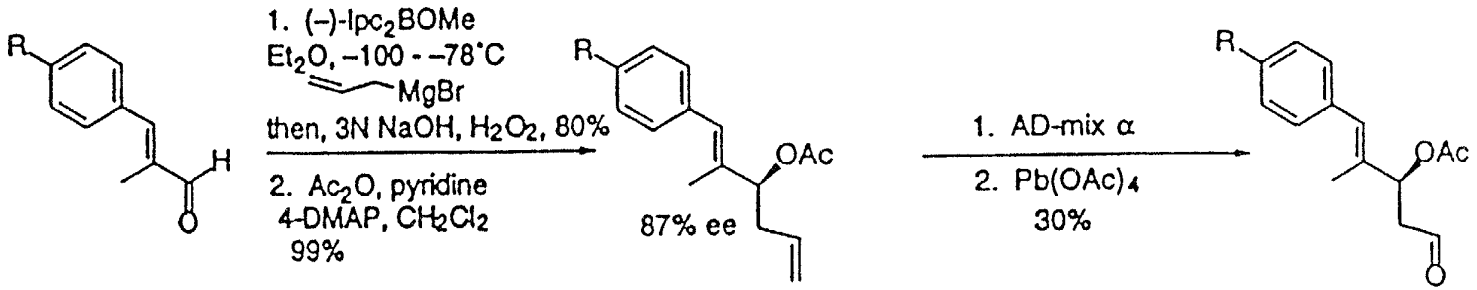
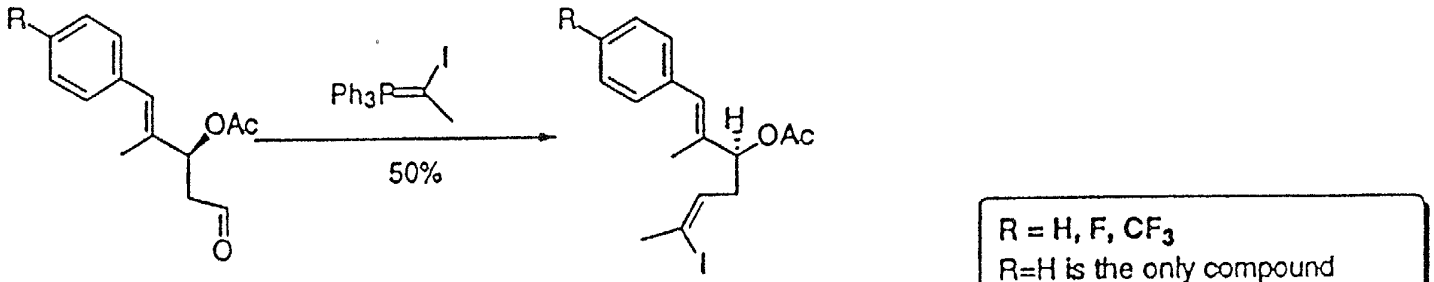


FIG. 26B



R = H, F, CF_3
R=H is the only compound completed, F and CF_3 are nearly completed

FIG. 26C

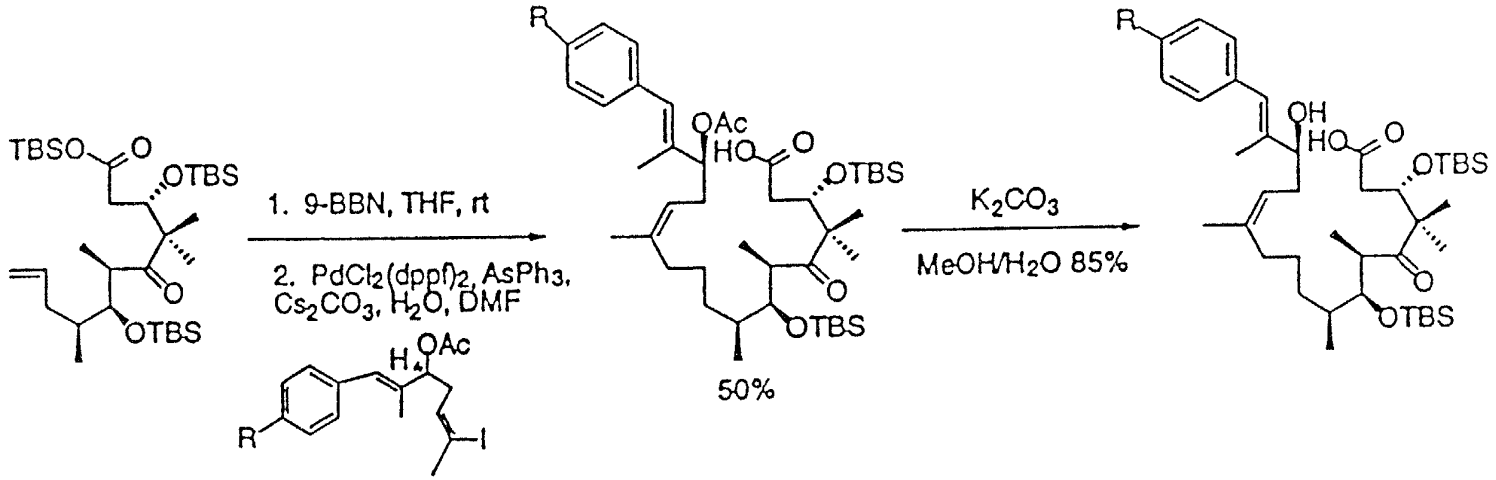
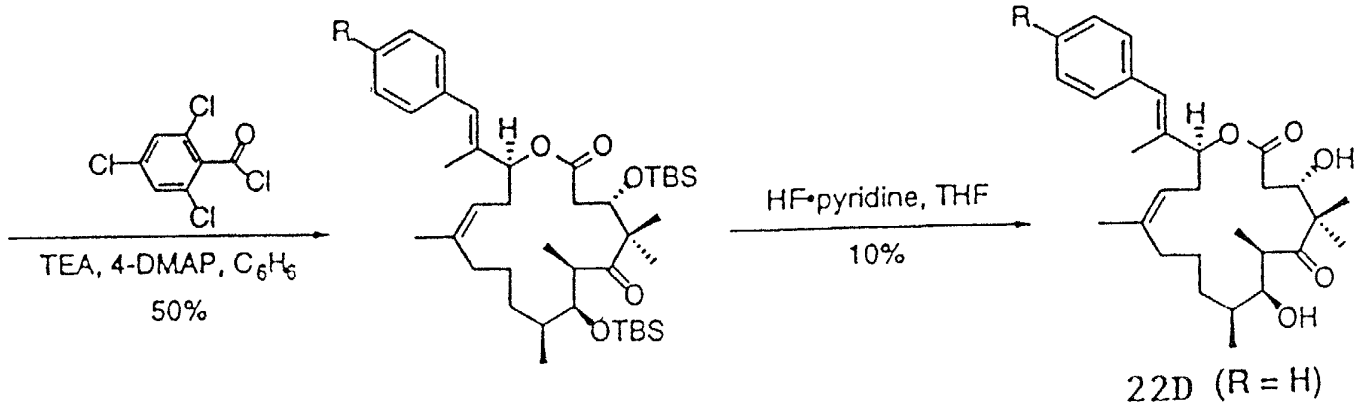


FIG. 26D



22D (R = H)

FIG. 27A

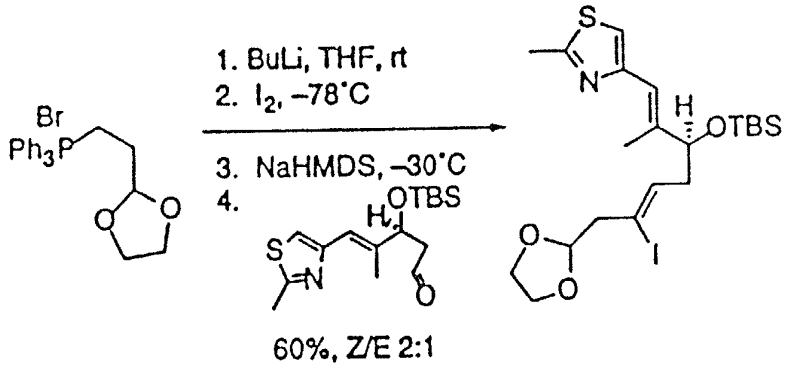


FIG. 27B

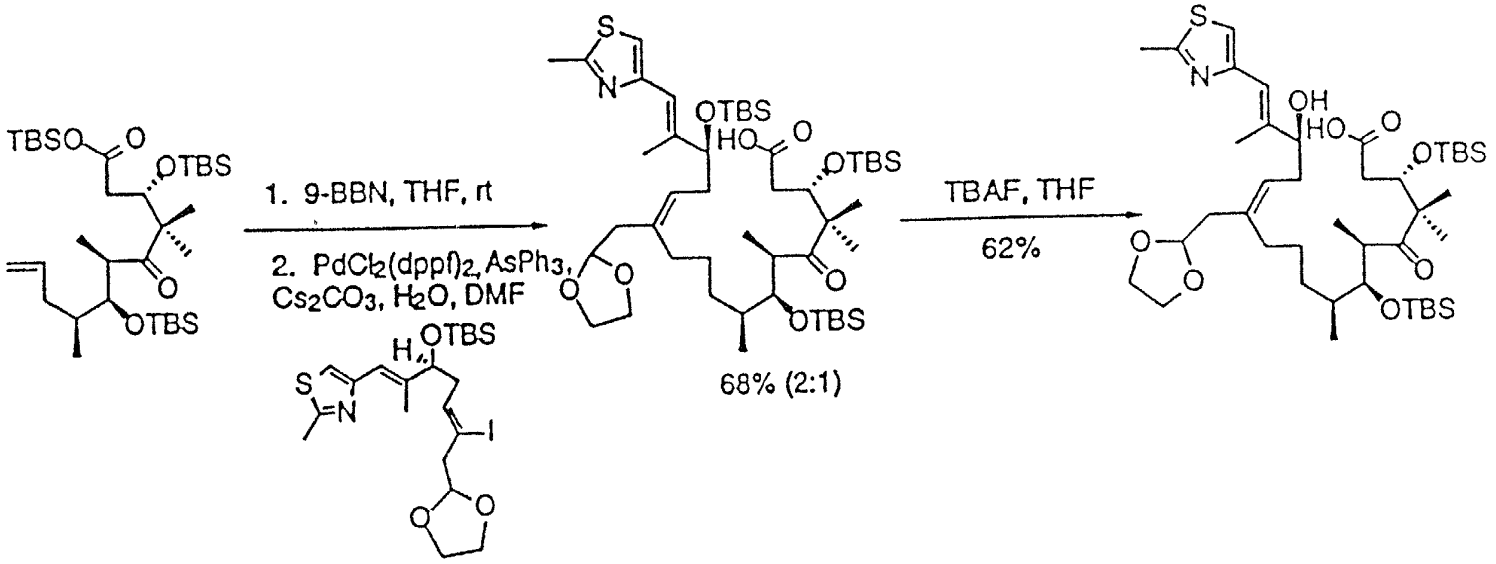


FIG. 27C

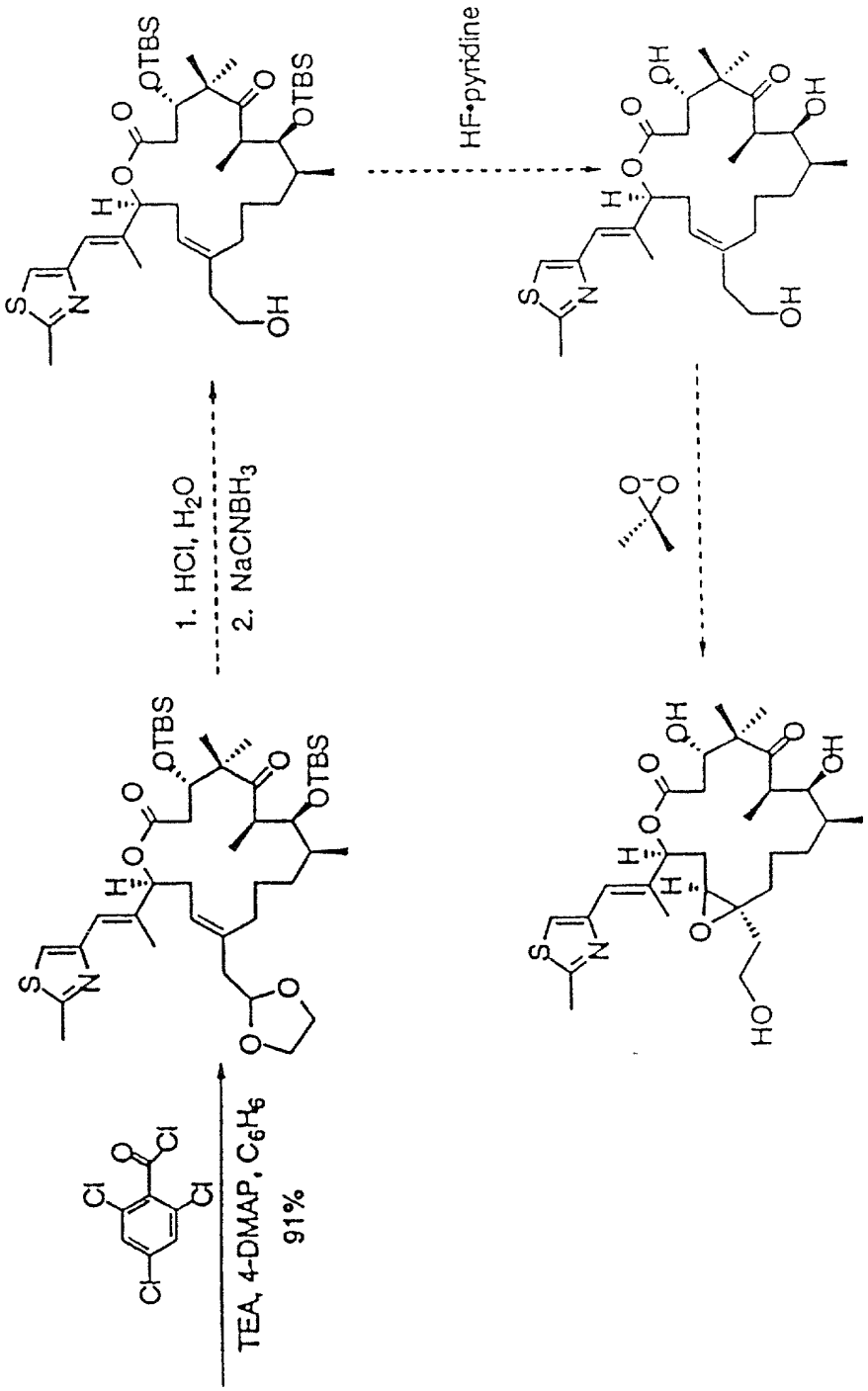

OTBS
OTBS
OH
1. HCl, H2O
2. NaCNBH3
HF•pyridine
OH
OH
OH
TEA, 4-DMAP, C6H6
91%
OTBS
OTBS
OH
OH
OH
HO

FIG. 28A

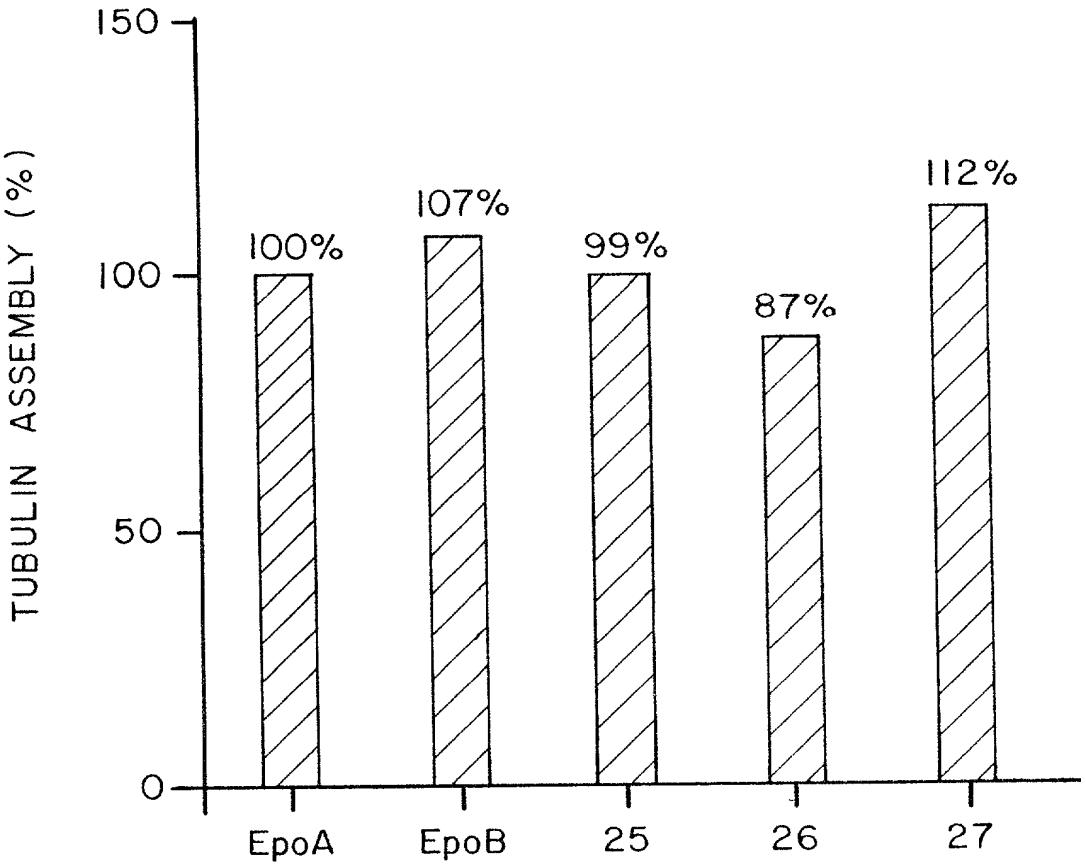

TUBULIN ASSEMBLY (%)
150
100
50
0
100%
107%
99%
87%
112%
EpoA
EpoB
25
26
27

FIG. 28B

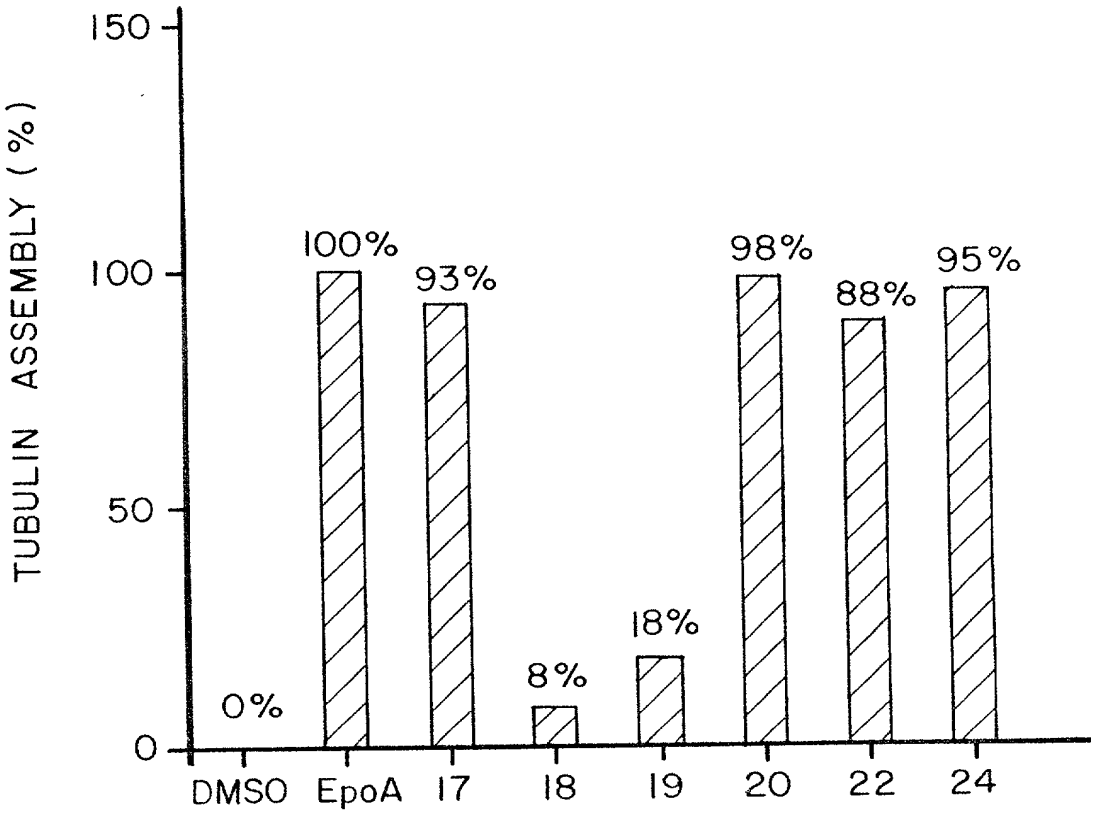

TUBULIN ASSEMBLY (%)
150
100
50
0
0%
100%
93%
8%
18%
98%
88%
95%
DMSO
EpoA
17
18
19
20
22
24

FIG. 29

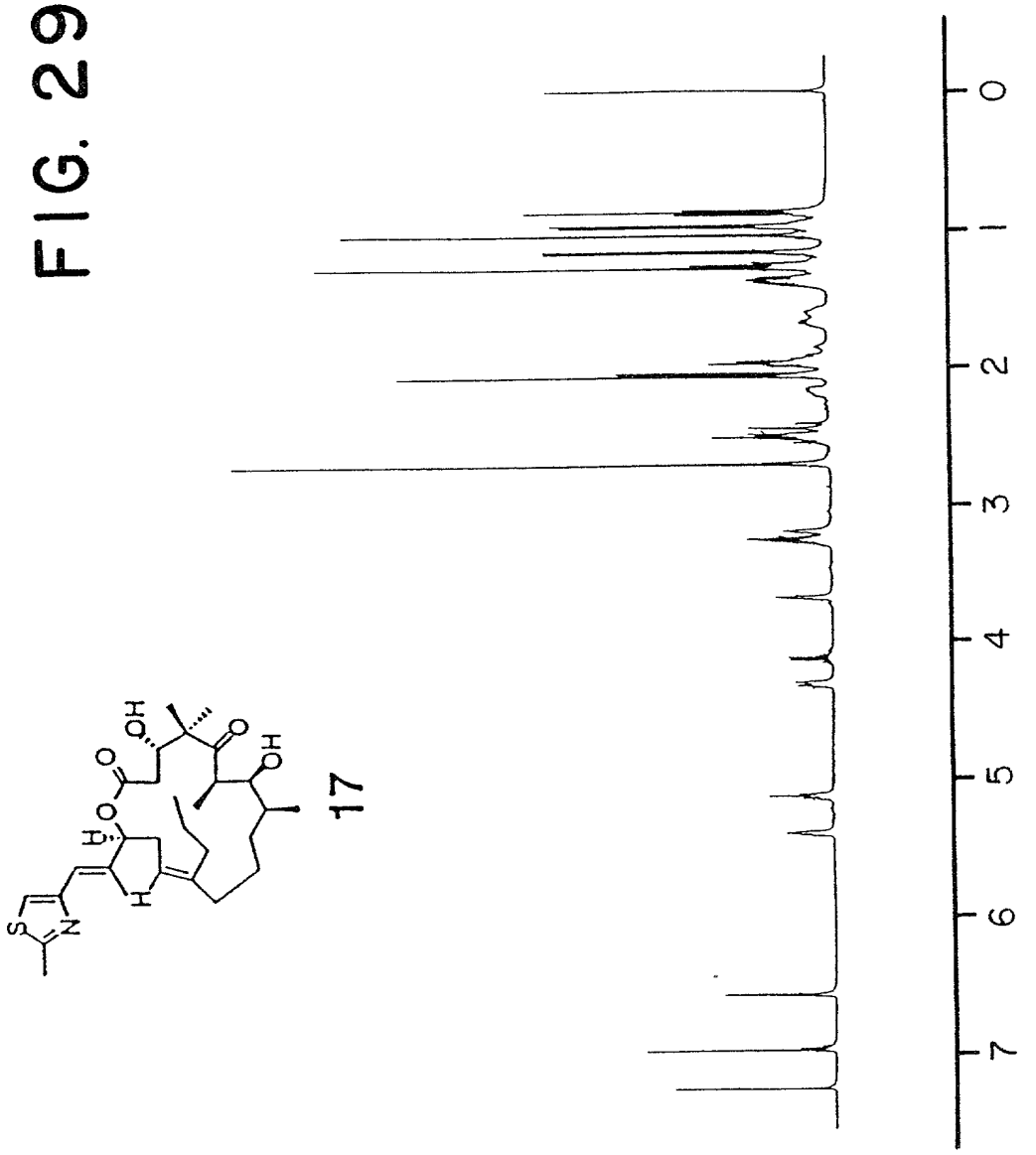


FIG. 30

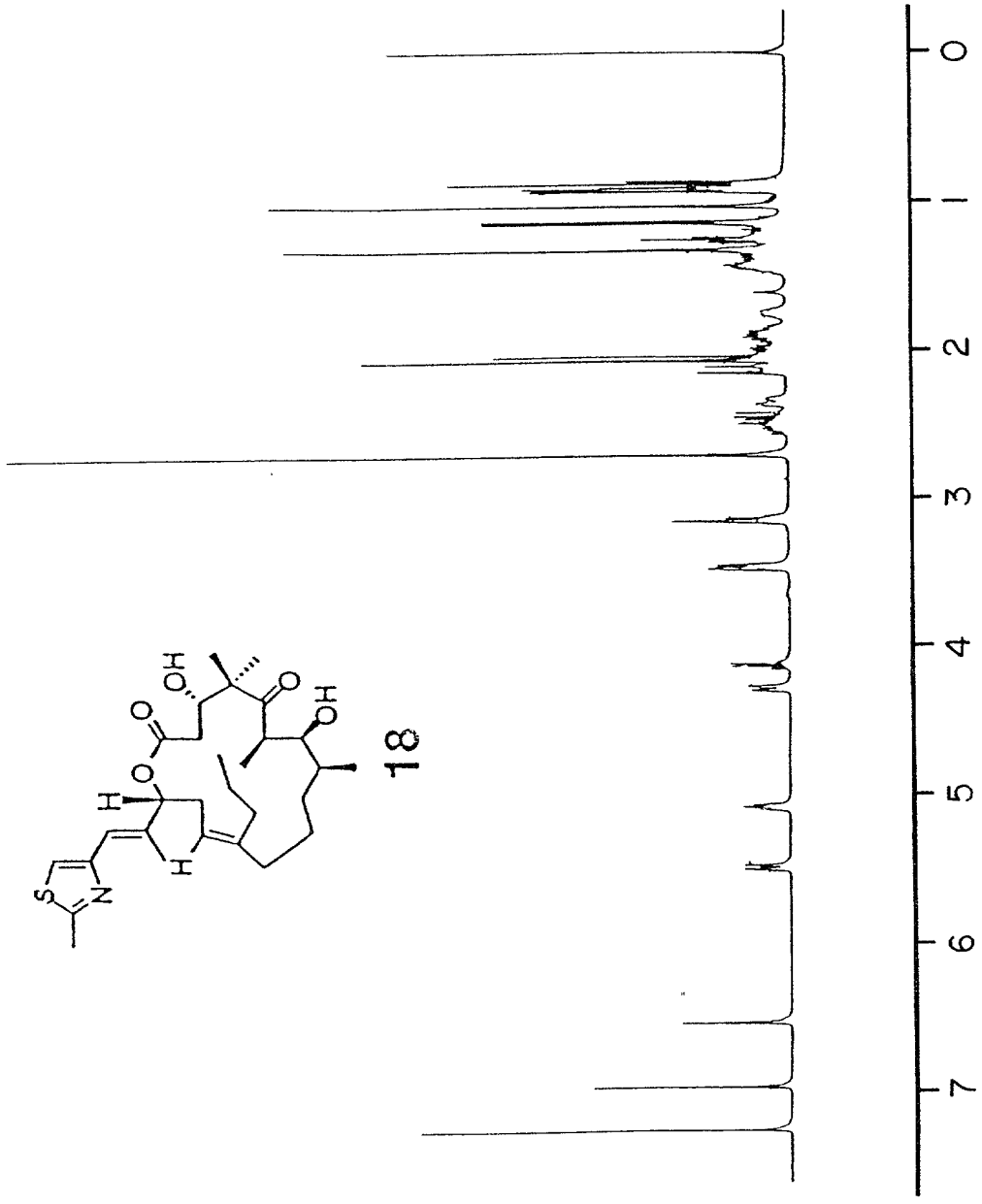
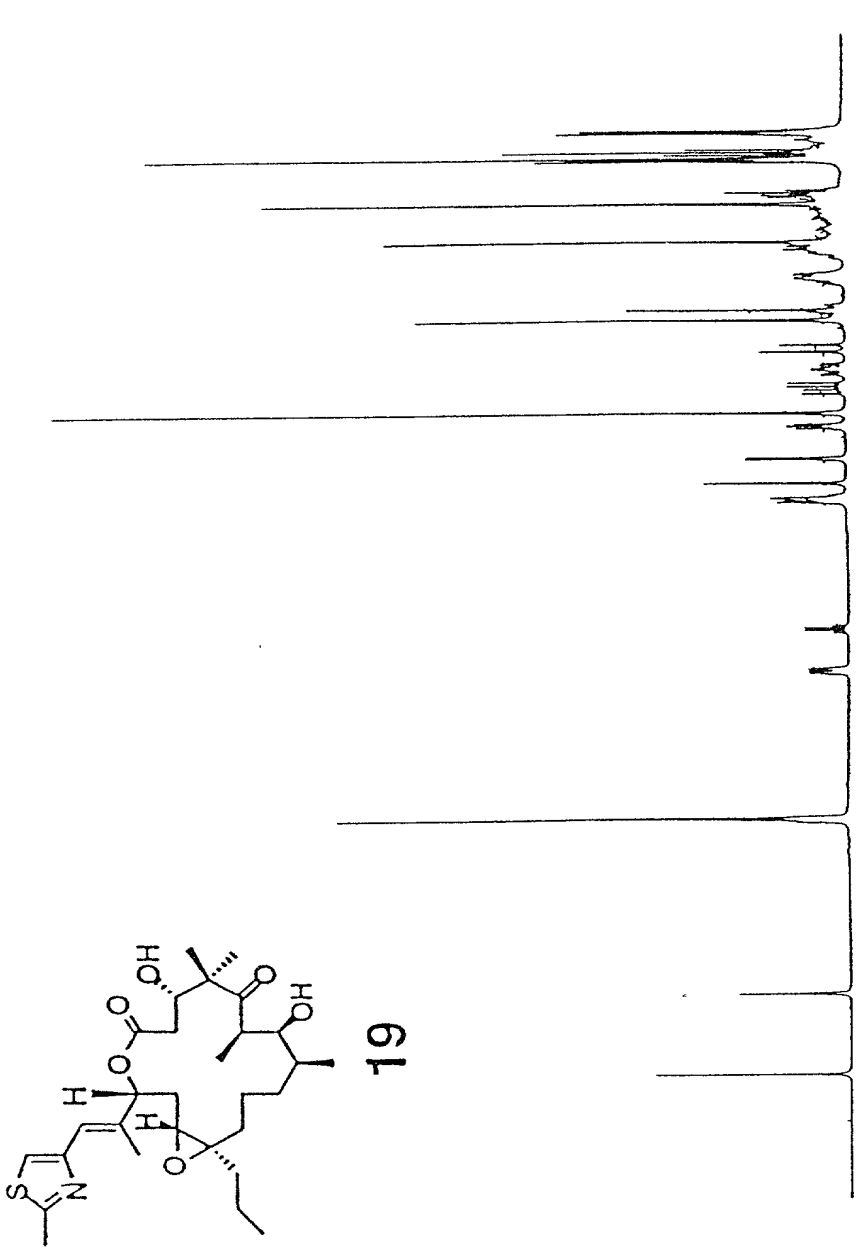
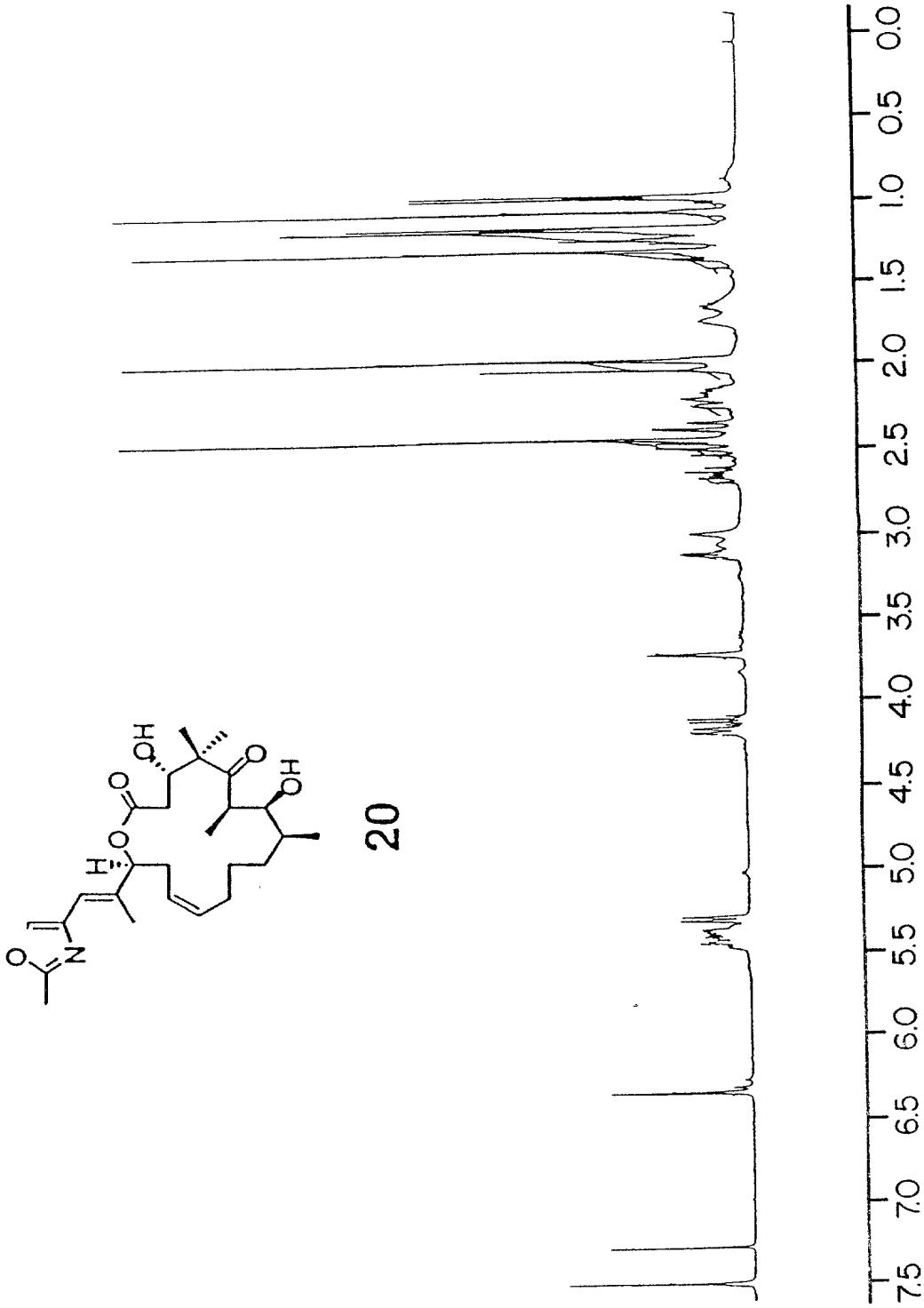


FIG. 31



19

FIG. 32



Replacement Sheet

FIG. 33

22

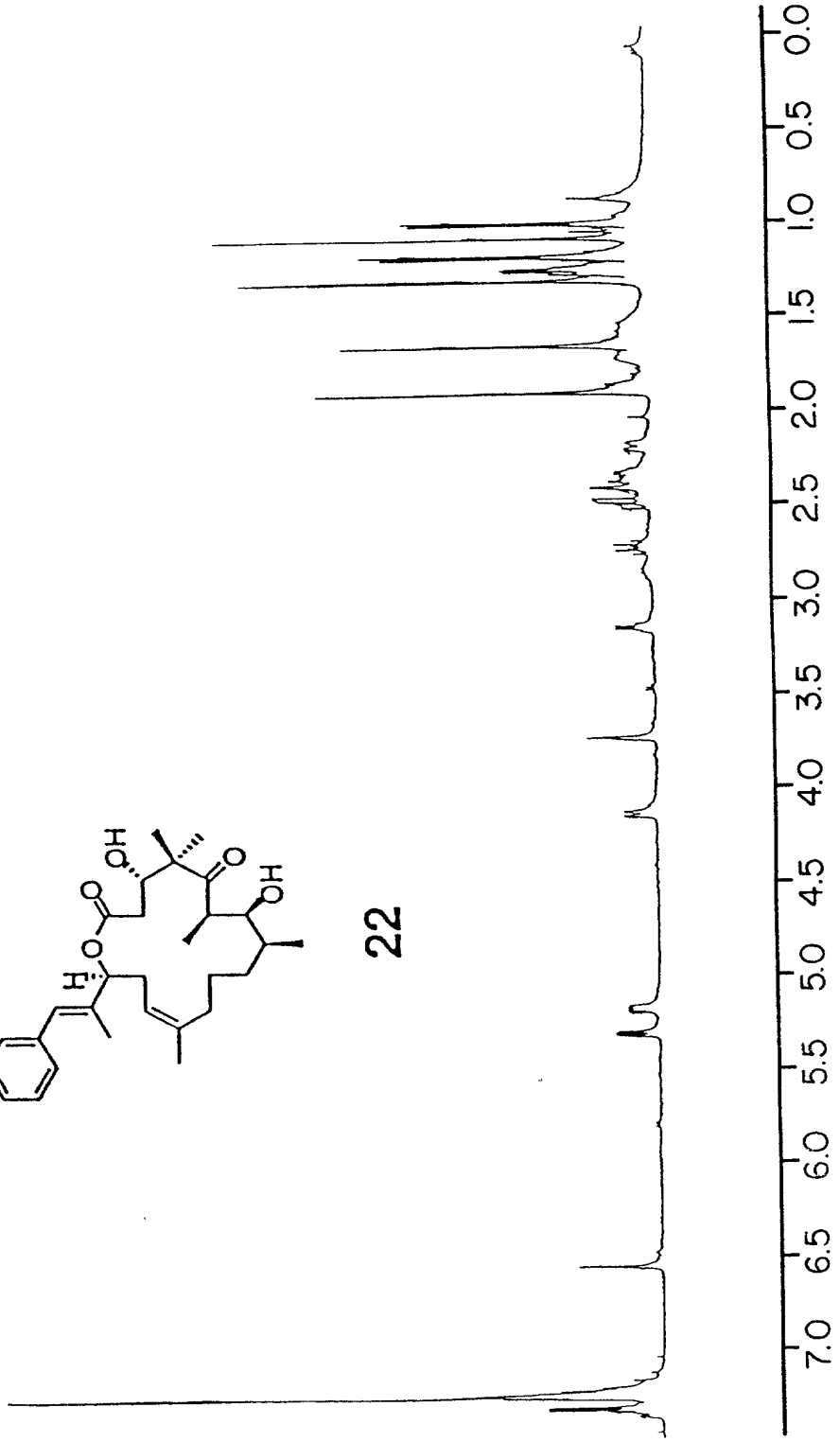


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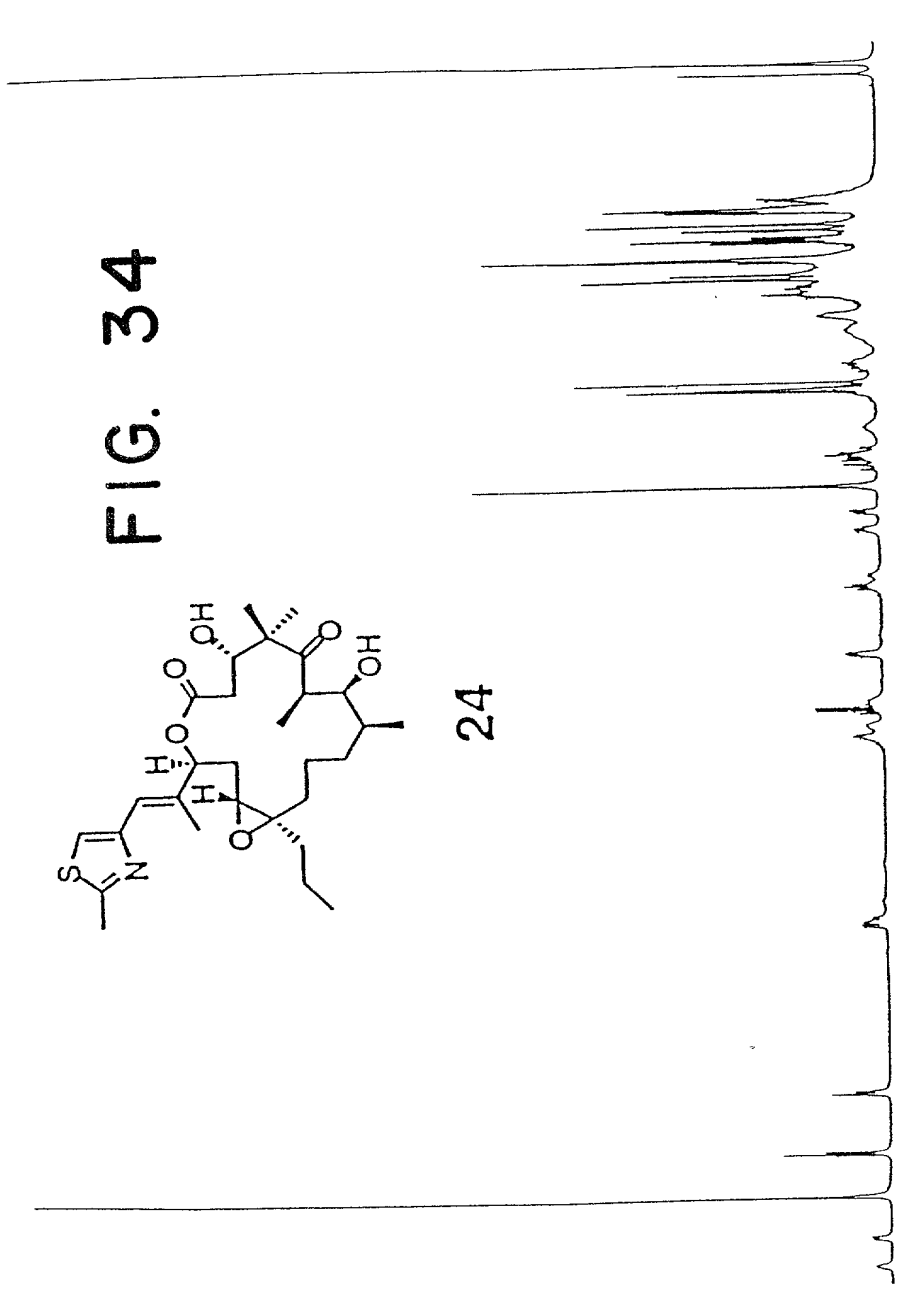
FIG. 34



24

FIG. 35

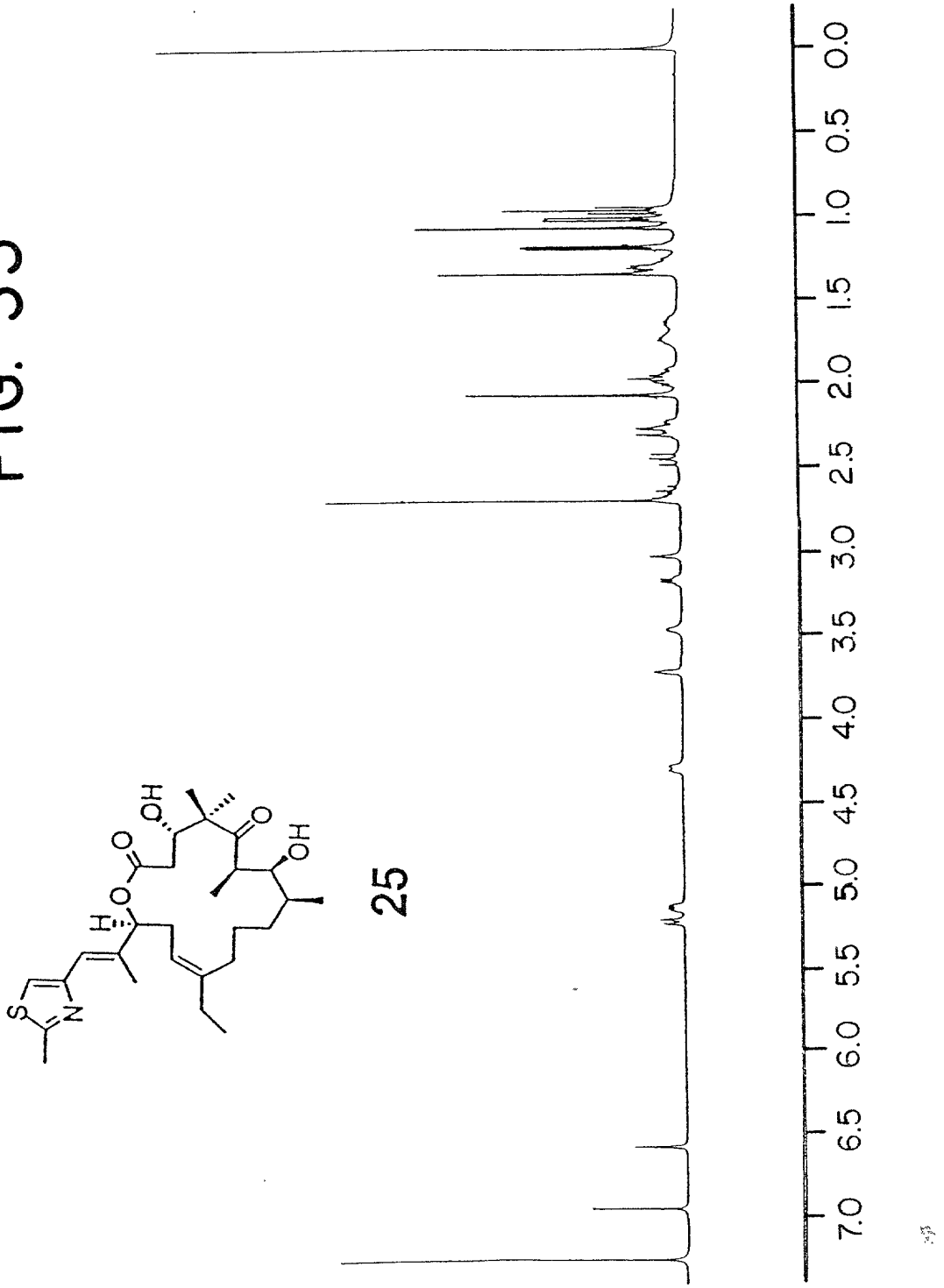
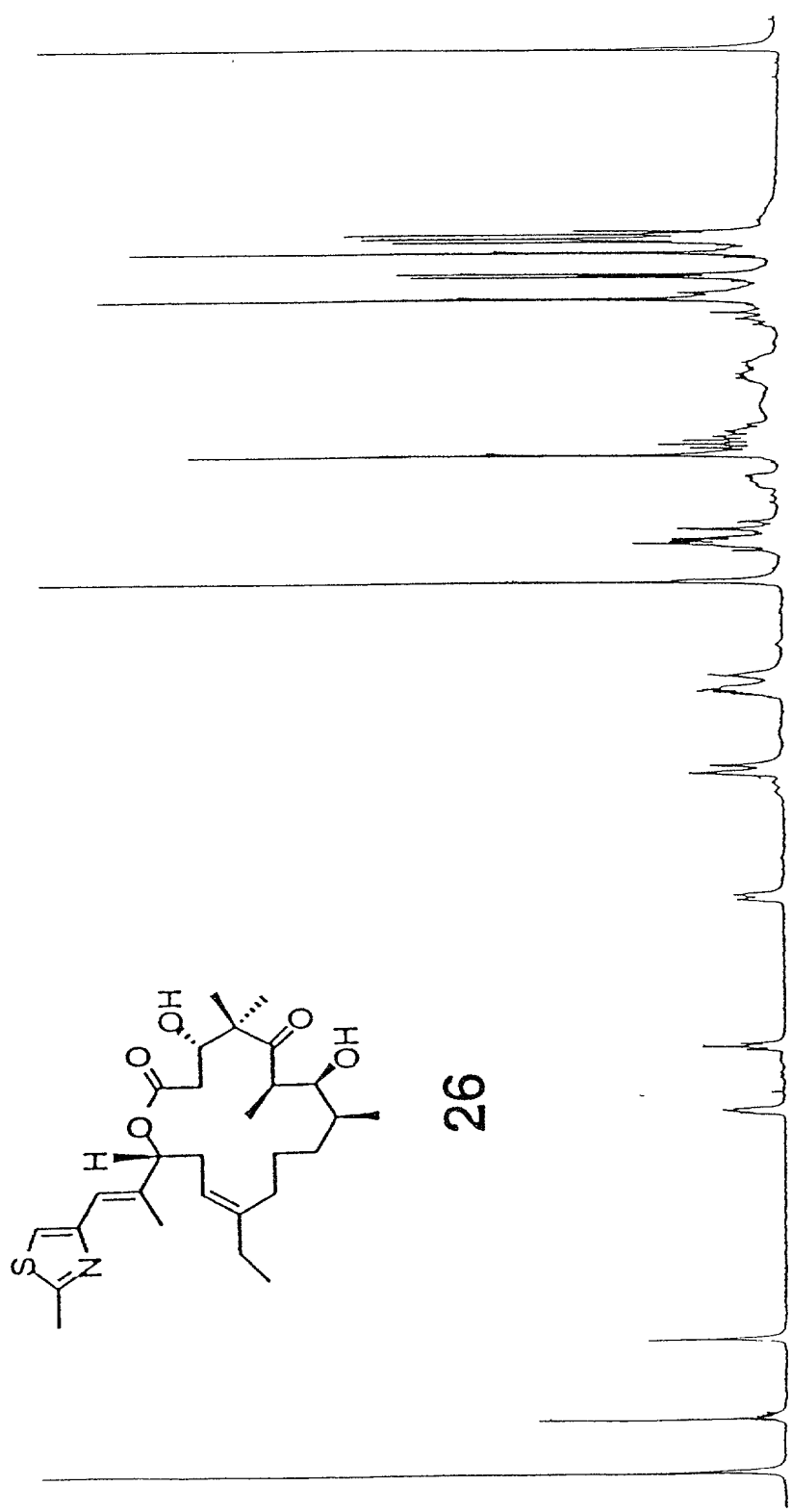


FIG. 36



26

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FIG. 37

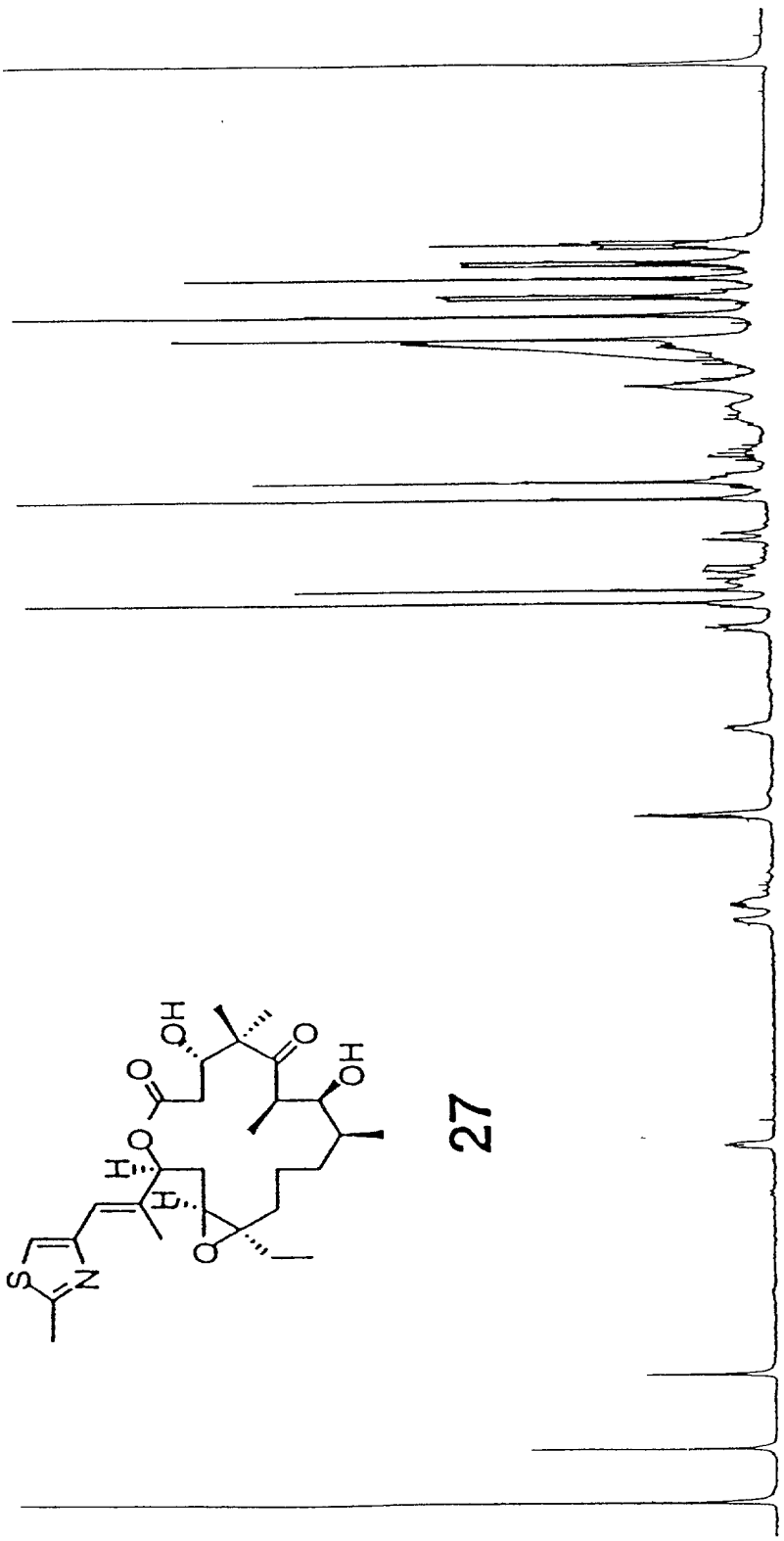
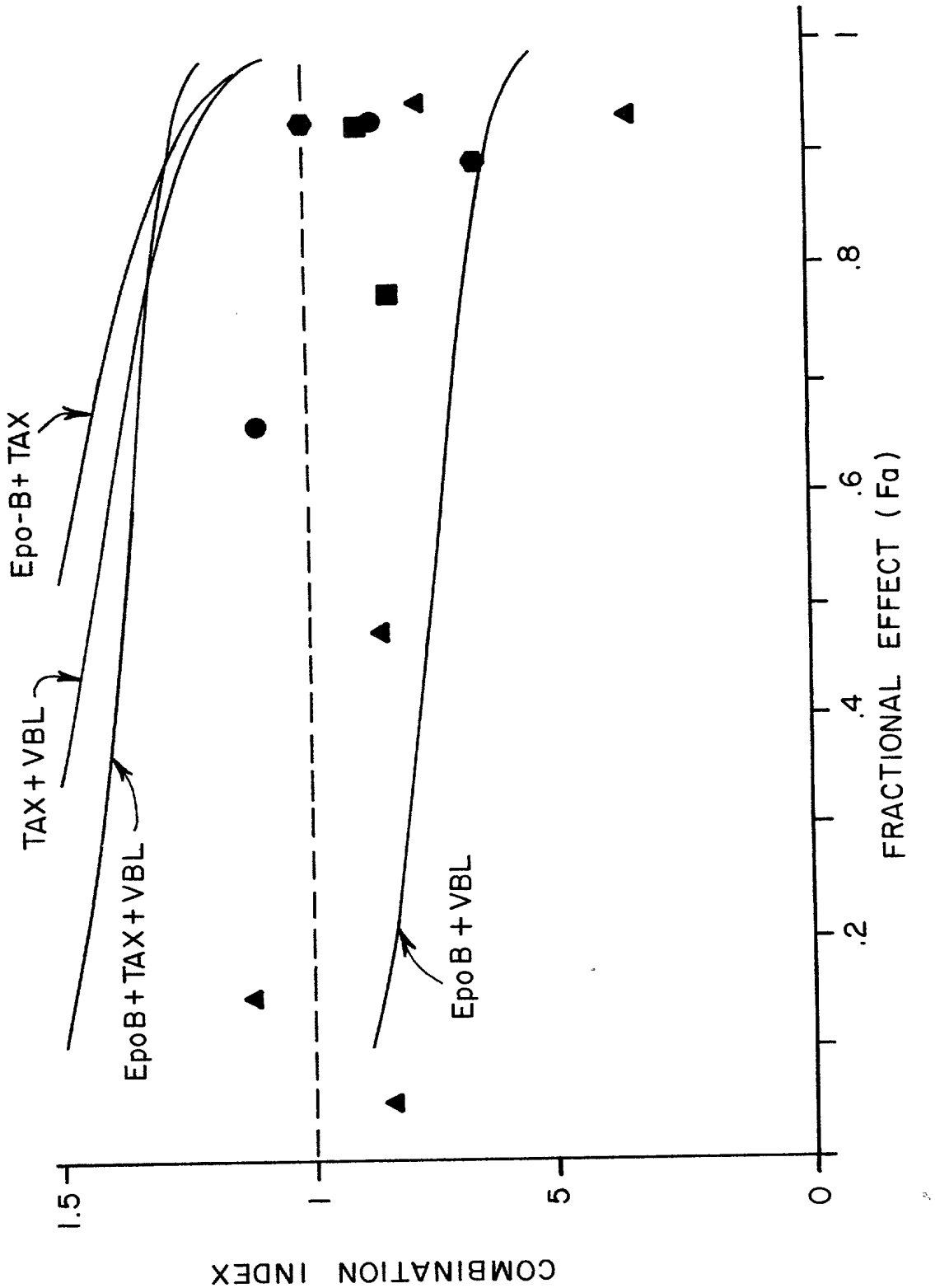
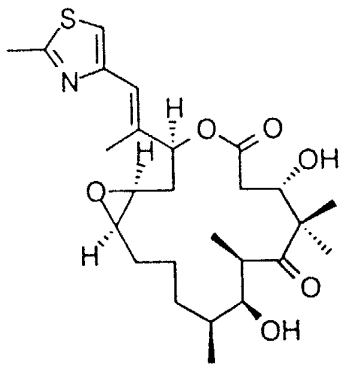
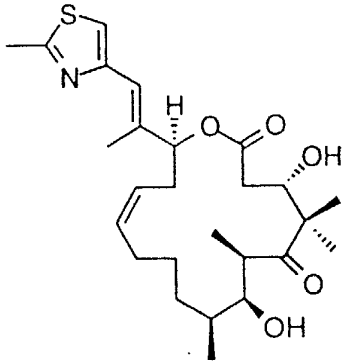


FIG. 38


Epo-B+ TAX
TAX + VBL
EpoB + TAX + VBL
EpoB + VBL
COMBINATION INDEX
1.5
1
.5
0
FRACTIONAL EFFECT (Fa)
.2
.4
.6
.8
1



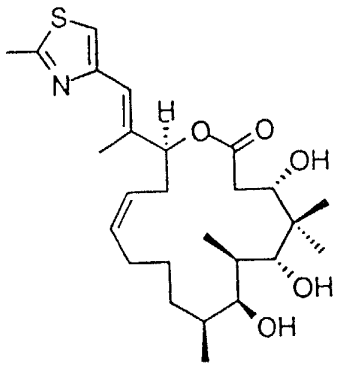
epothilone A
(0.0027)
[0.020]



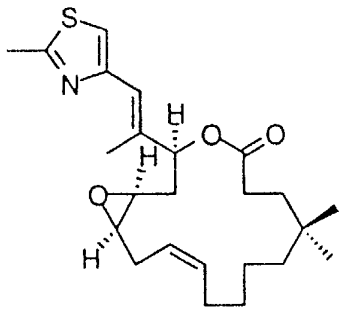
desoxyepothilone A

1
(0.022)
[0.012]

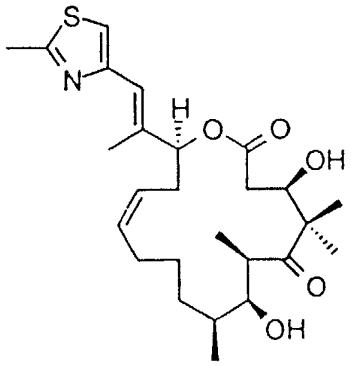
FIG. 39A



2
(14.23)
[6.28]

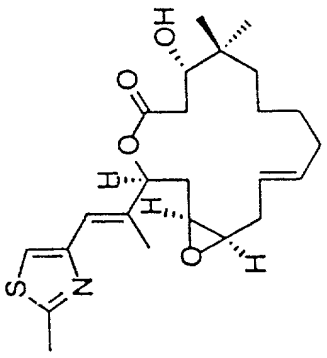


3
(271.1)
[22.4]

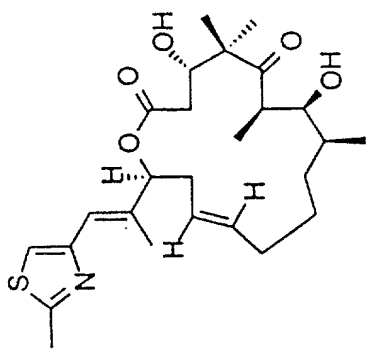


4
(2.12)
[43.0]

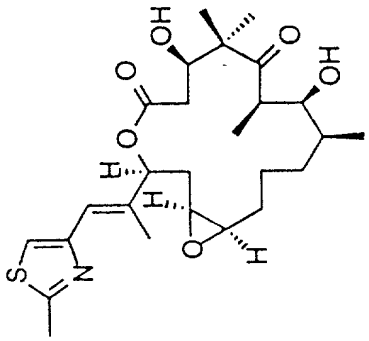
FIG. 39B



7
(7.36)
[9.82]

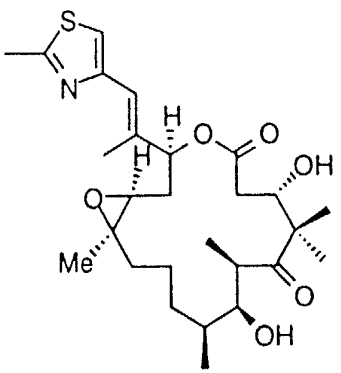


6
(0.052)
[0.035]



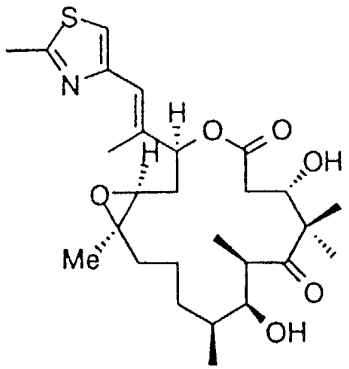
5
(>20)
[35.2]

FIG. 40A



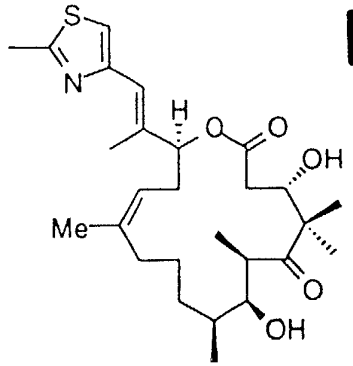
synthetic epothilone B

8
(0.00044)
[0.0026]



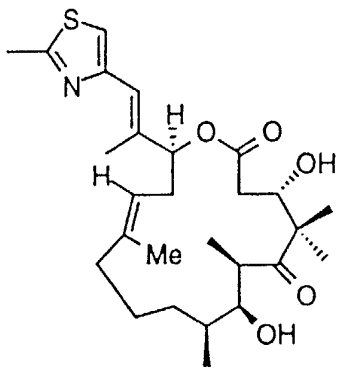
natural epothilone B

9
(0.00017)
[0.0012]

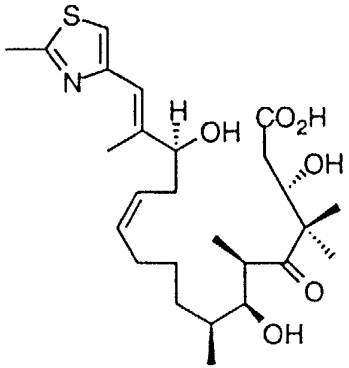


desoxyepothilone B

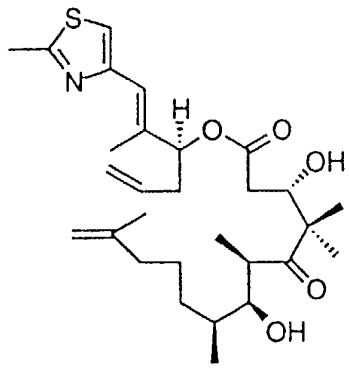
10
(0.0095)
[0.017]



11
(0.090)
[0.262]

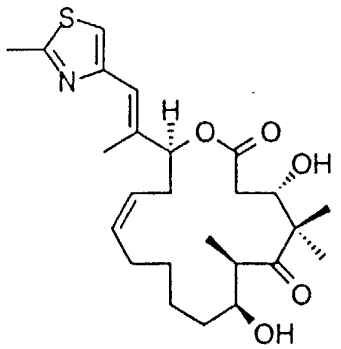


12
(0.79)
[>5]

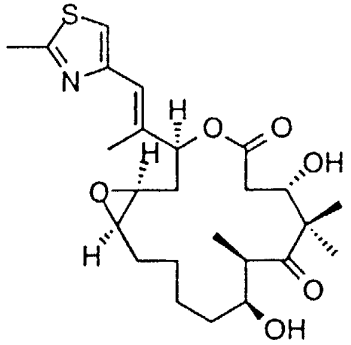


13
(11.53)
[5.63]

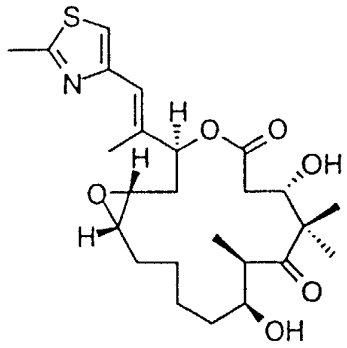
FIG. 40B



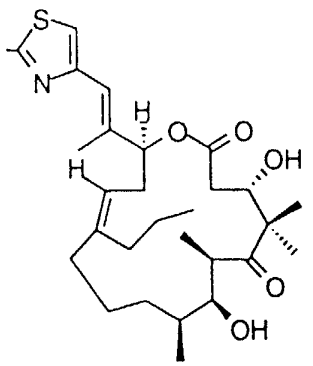
14
(5.42)
[5.75]



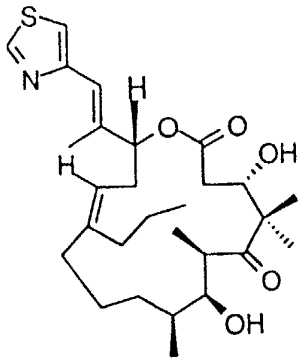
15
(0.96)
[5.95]



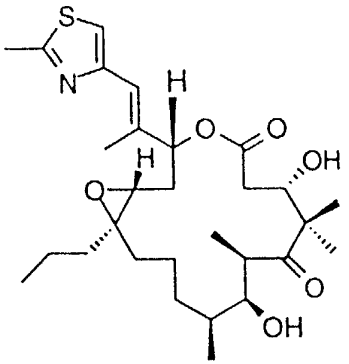
16
(7.47)
[16.48]



17
(0.090)
[0.254]

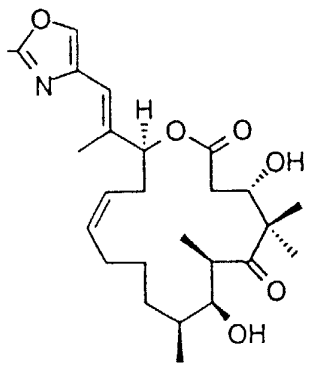


18
(1158)
[>720]

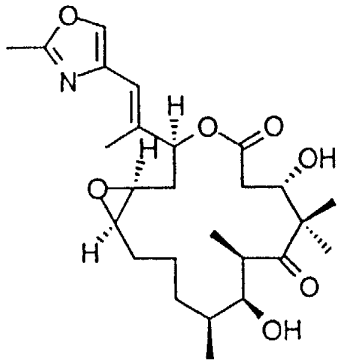


19
(0.96)
[>1.0]

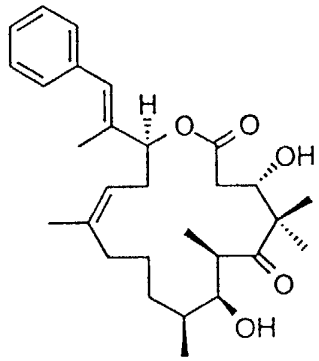
FIG. 41A



20
(0.030)
[0.049]



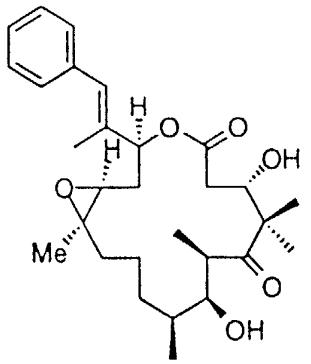
21



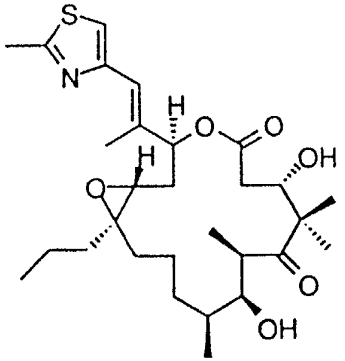
22
(0.098)
[0.146]

TOHOZF" FZSHOOOF

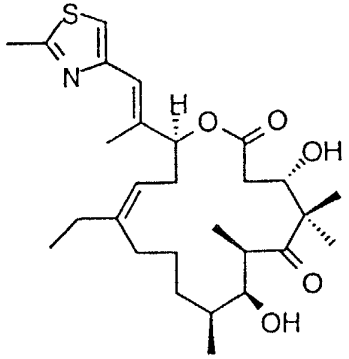
FIG. 41B



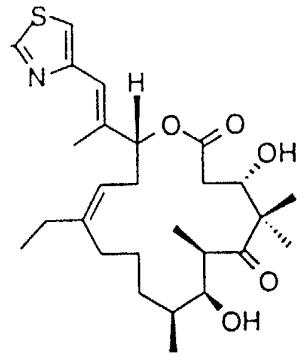
23



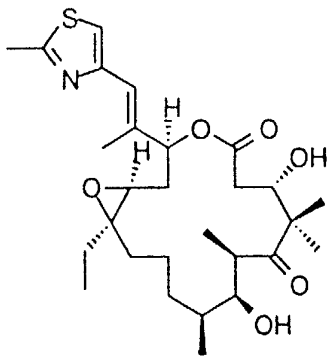
24
(0.0043)
[0.032]



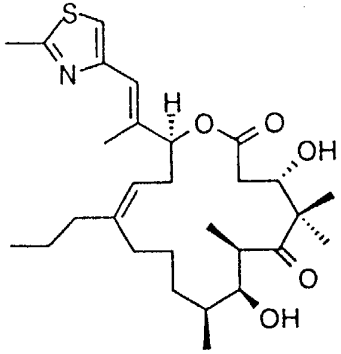
25
(0.021)
[0.077]



26
(0.055)
[0.197]

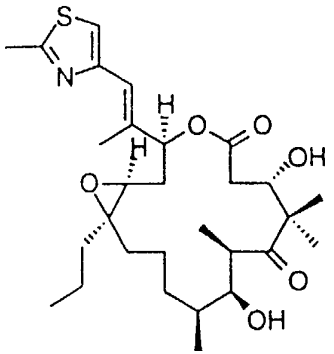


27
(0.0010)
[0.0072]

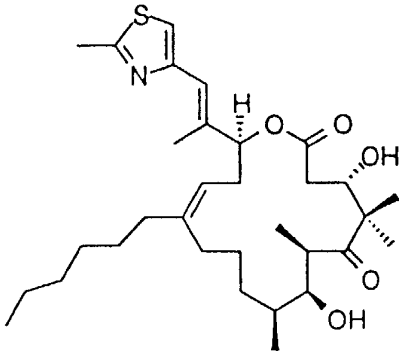


28
(0.039)
[0.067]

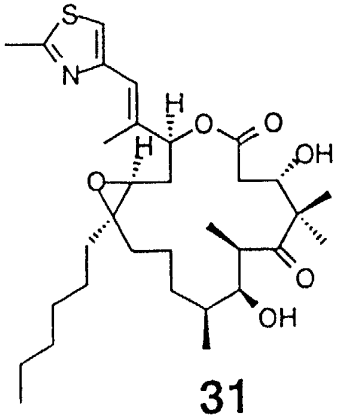
FIG. 42A



29
(0.0038)
[0.0064]

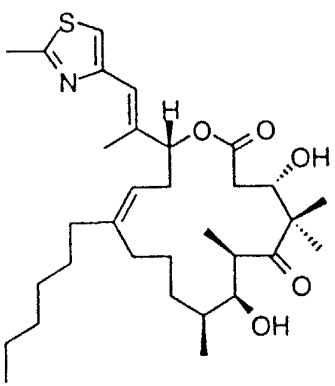


30
(0.044)
[0.108]

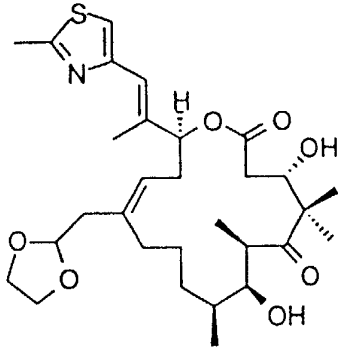


31
(0.027)
[0.049]

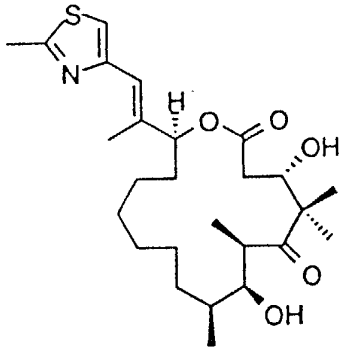
FIG. 42B



32
(0.063)
[0.380]

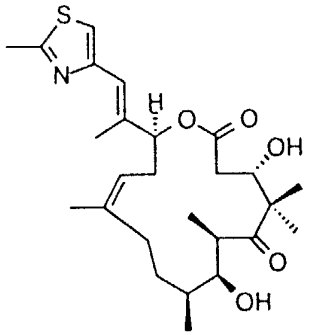


33
(0.0031)
[0.0093]

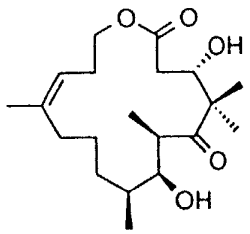


34
(0.143)
[0.276]

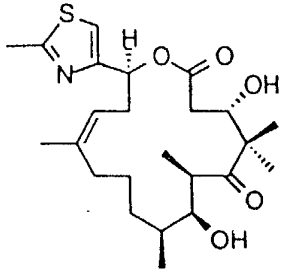
FIG. 42C



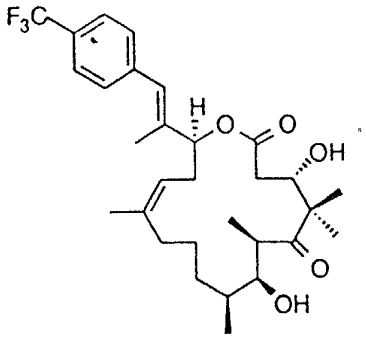
35
(>10)
[8.95]



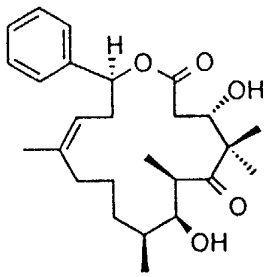
36
(234.5)
[>10]



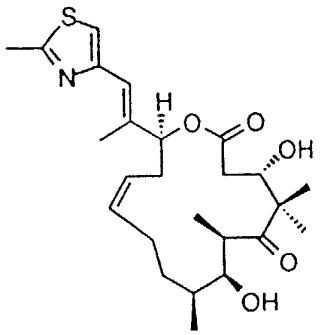
37
(3.25)
[1.20]



38
(0.254)
[>5.0]

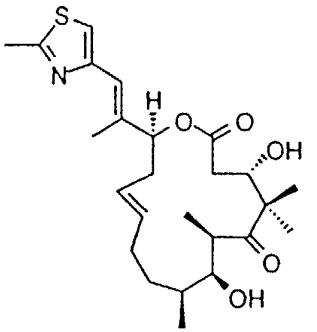


39
(1.80)
[>5.0]

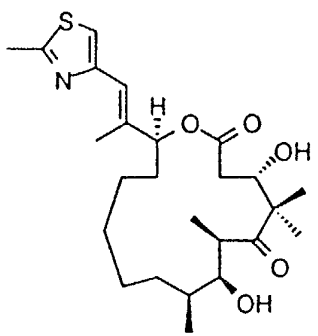


40
(36.9)
[47.3]

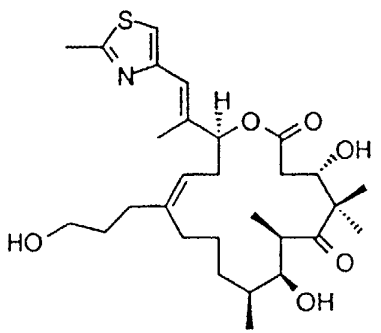
FIG. 42D



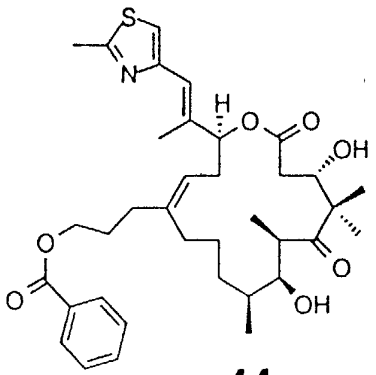
41
(60.1)
[59.2]



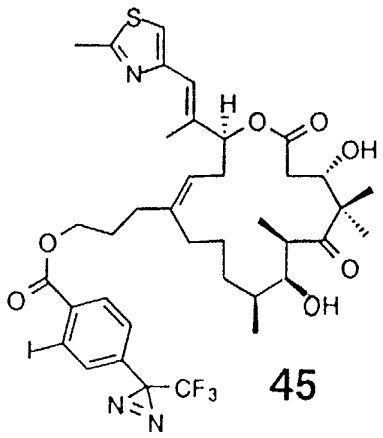
42
(7.41)
[12.9]



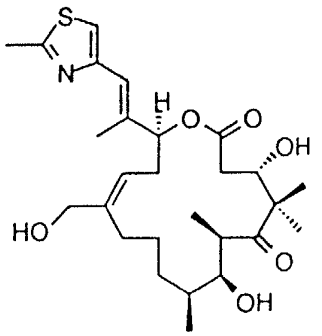
43
(0.0095)
[0.167]



44 (0.250)
[0.905]



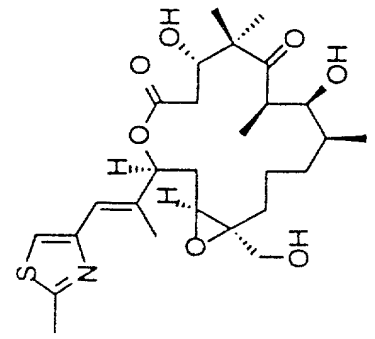
45



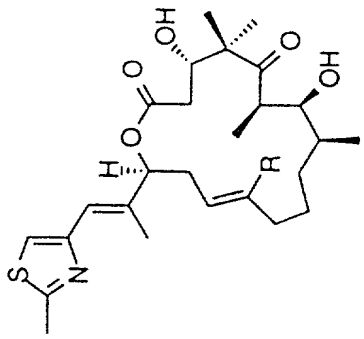
46 (0.049)
[>1.0]

Patent Application Publication

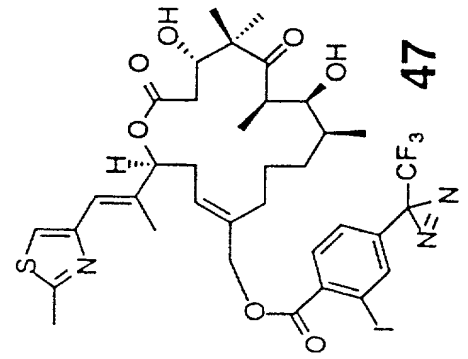
FIG. 42E



49



48 R = $(CH_2)_3OH$



47

FIG. 43A

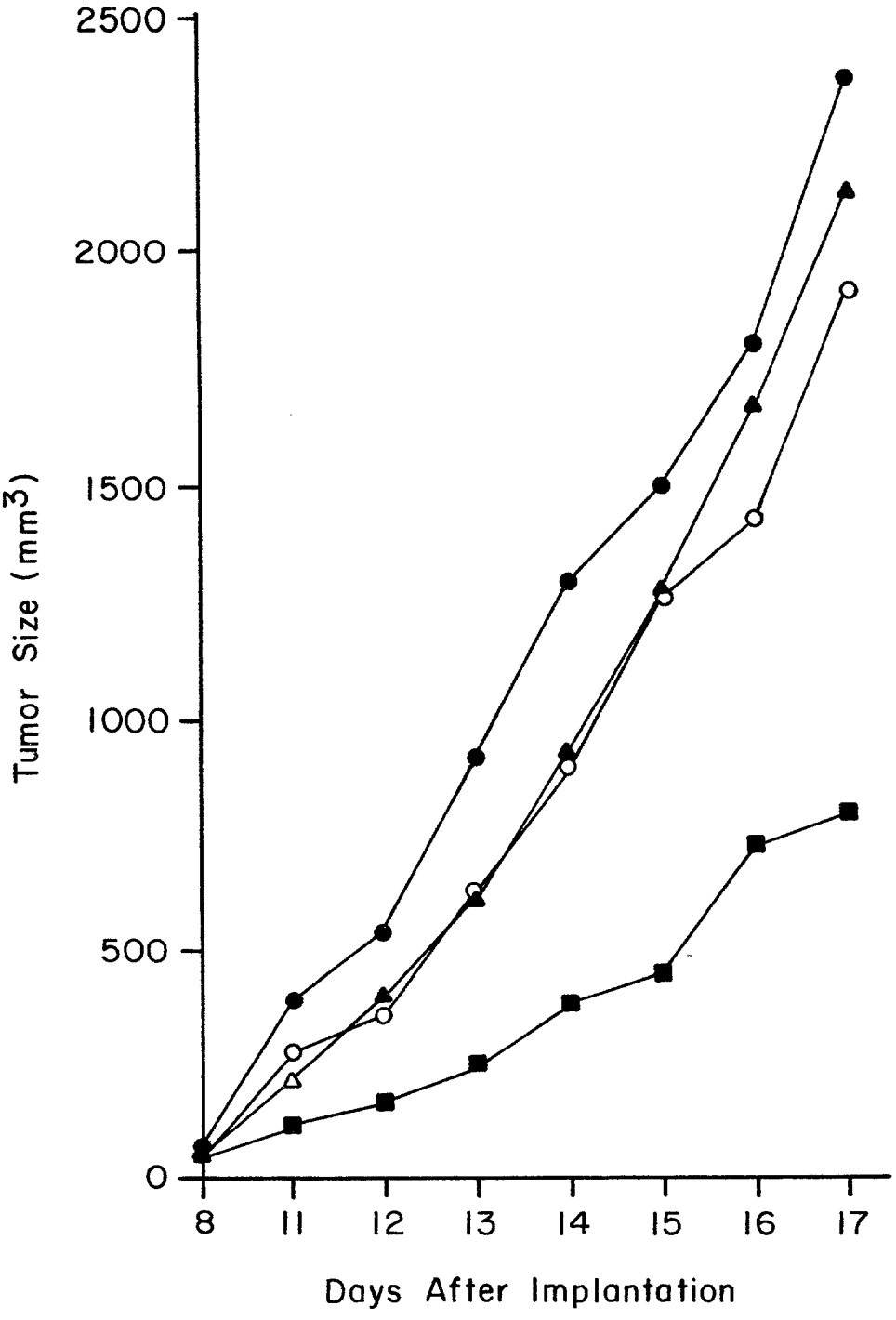

2500
2000
1500
1000
500
0
Tumor Size (mm3)
8
11
12
13
14
15
16
17
Days After Implantation

FIG. 43B

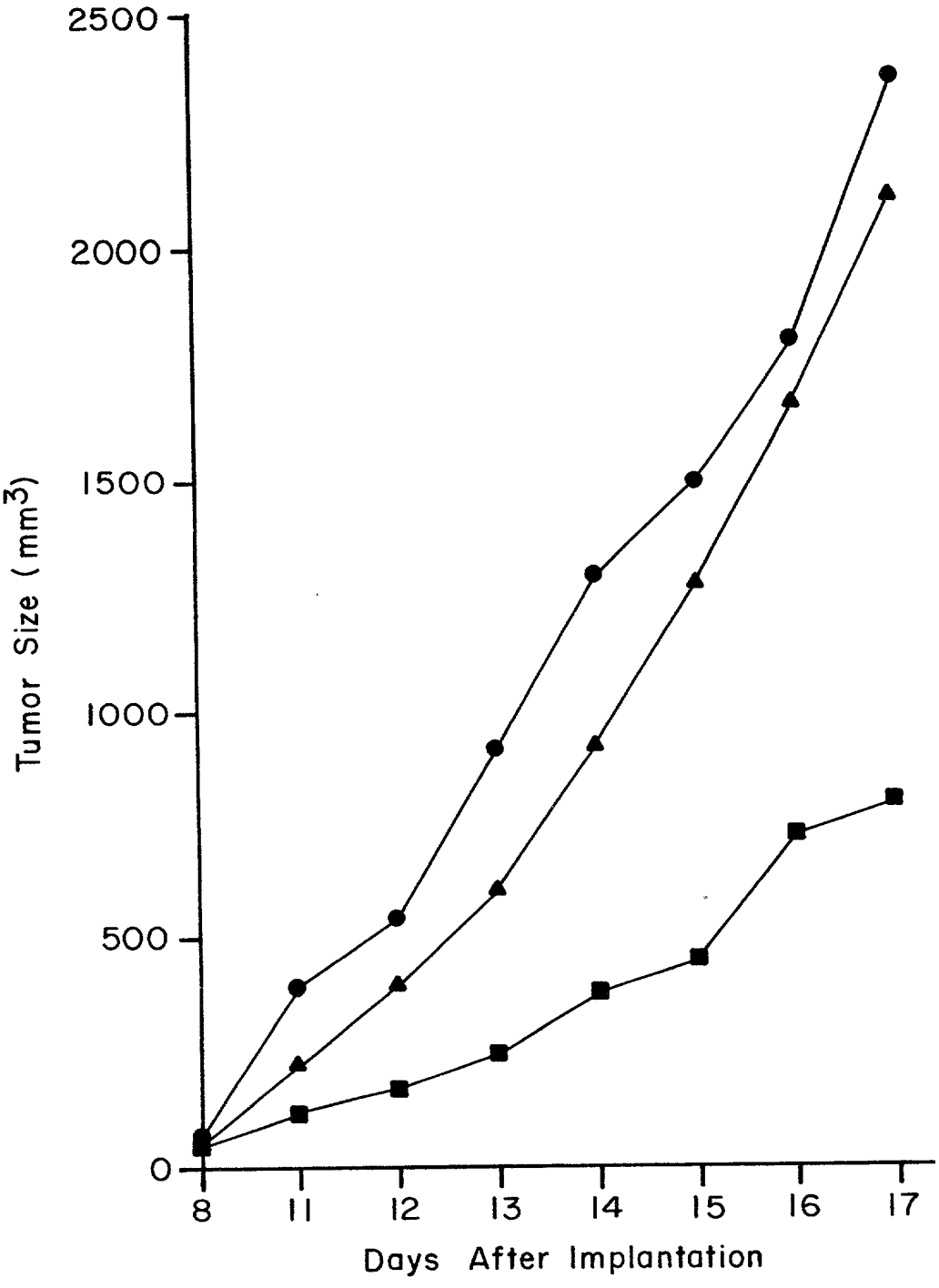

2500
2000
1500
1000
500
0
Tumor Size (mm3)
8
11
12
13
14
15
16
17
Days After Implantation

FIG. 44A

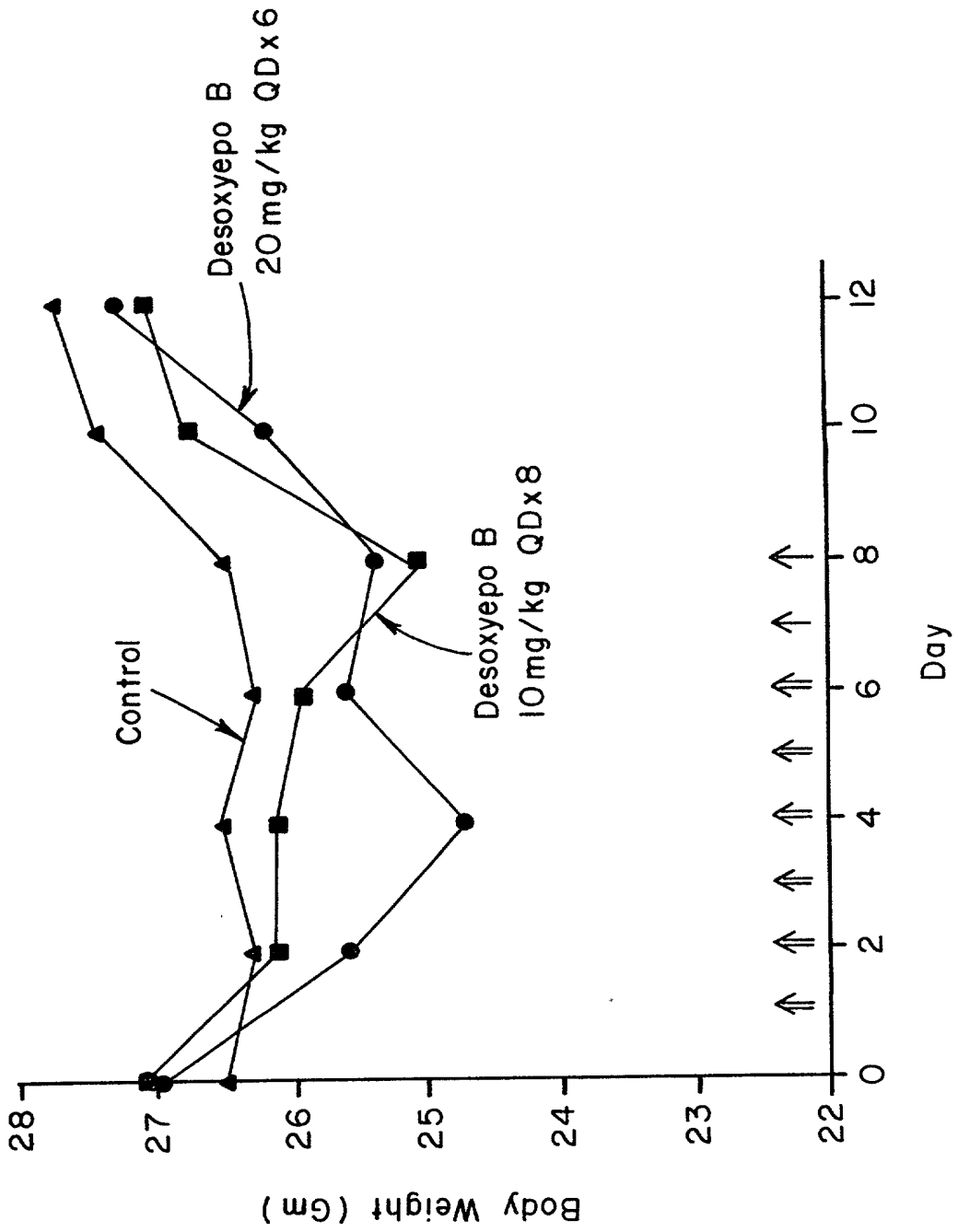

Desoxyepo B
20 mg/kg QDx6
Control
Desoxyepo B
10 mg/kg QDx8
Body Weight (Gm)
28
27
26
25
24
23
22
0
2
4
6
8
10
12
Day

FIG. 44B

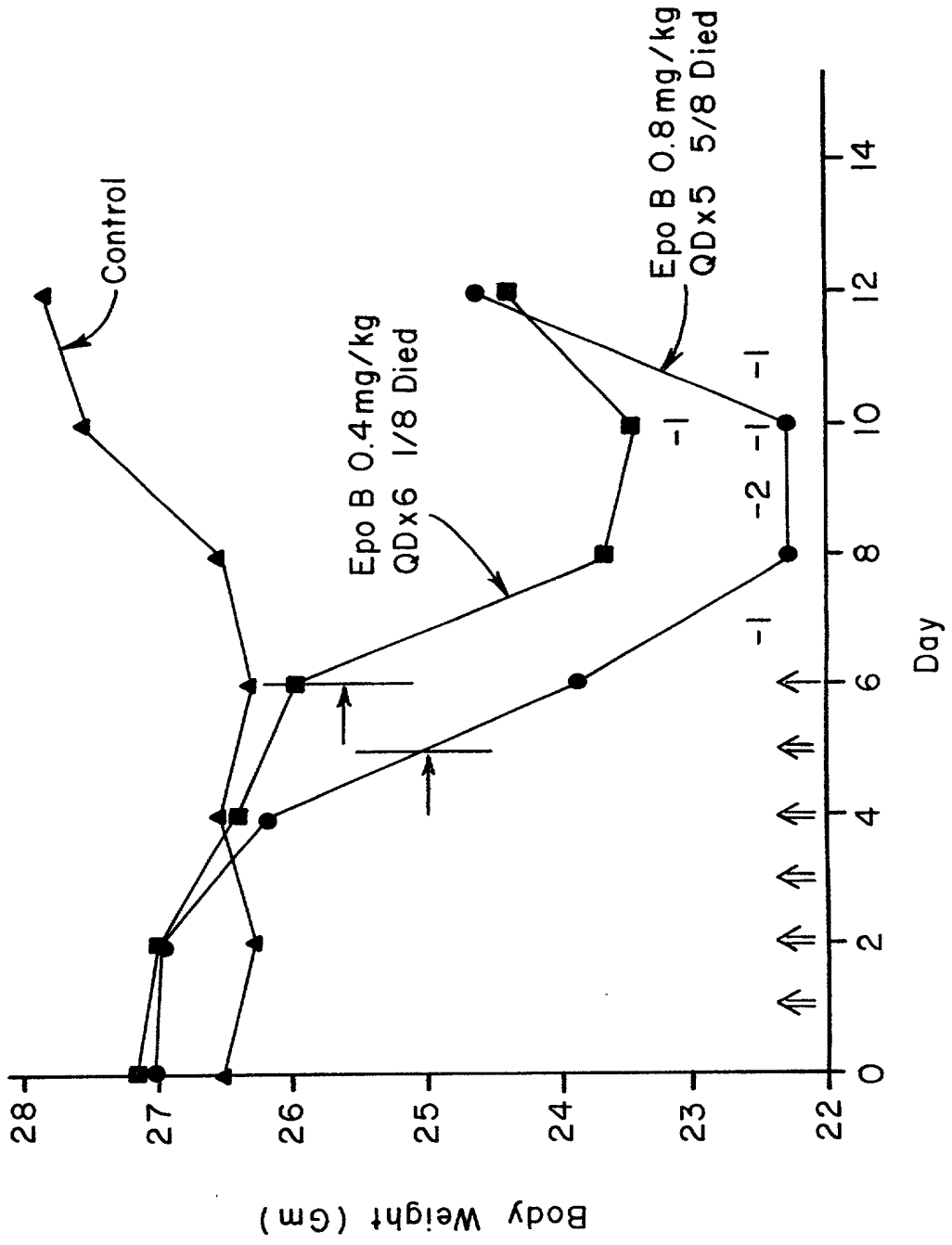

Control
Epo B 0.4mg/kg
QDx6 1/8 Died
Epo B 0.8mg/kg
QDx5 5/8 Died
-1
-1
-2
-1
-1
Body Weight (Gm)
Day
28
27
26
25
24
23
22
0
2
4
6
8
10
12
14

FIG. 45A

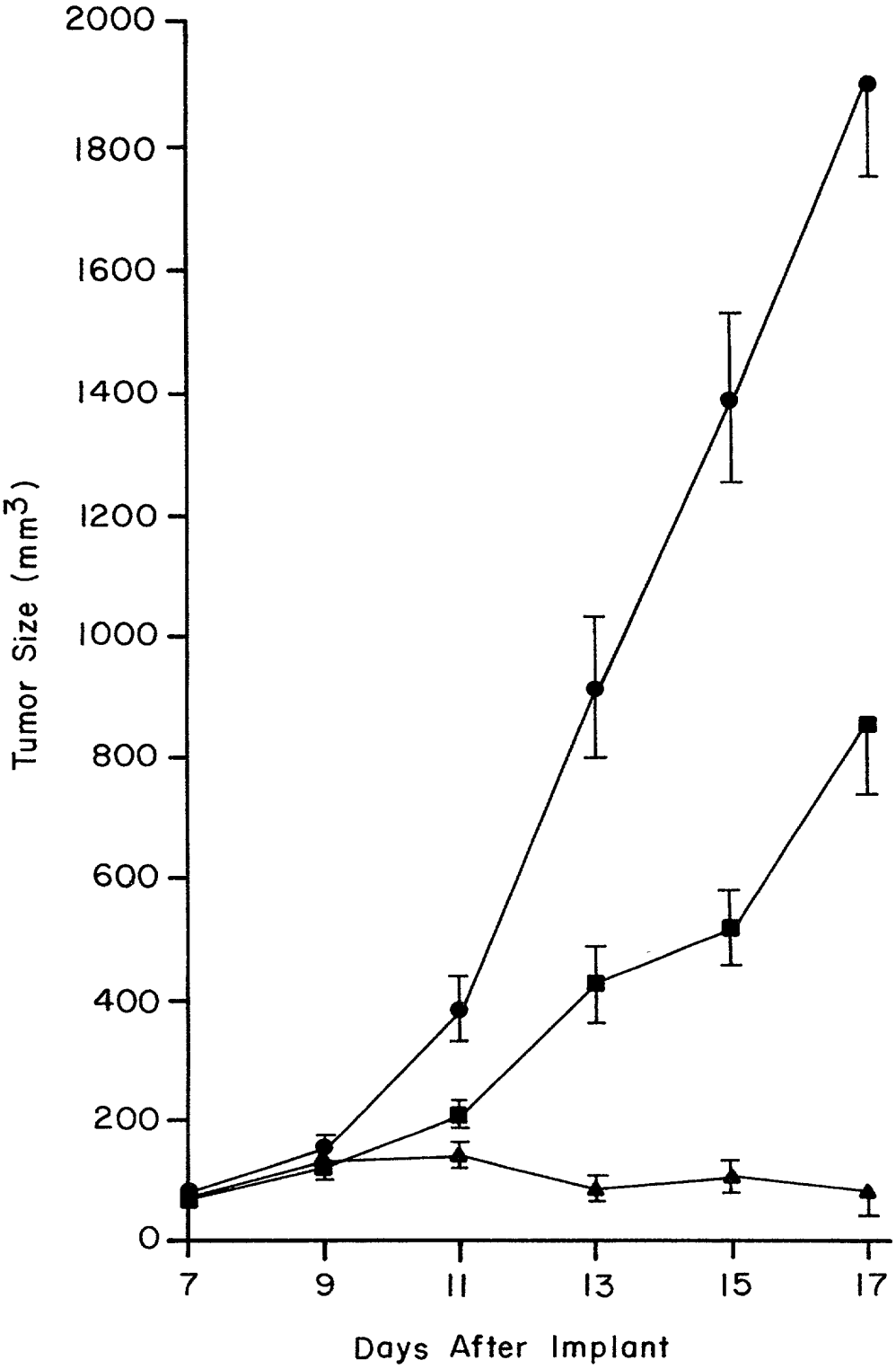

2000
1800
1600
1400
1200
1000
800
600
400
200
0
Tumor Size (mm3)
7
9
11
13
15
17
Days After Implant

FIG. 45 B

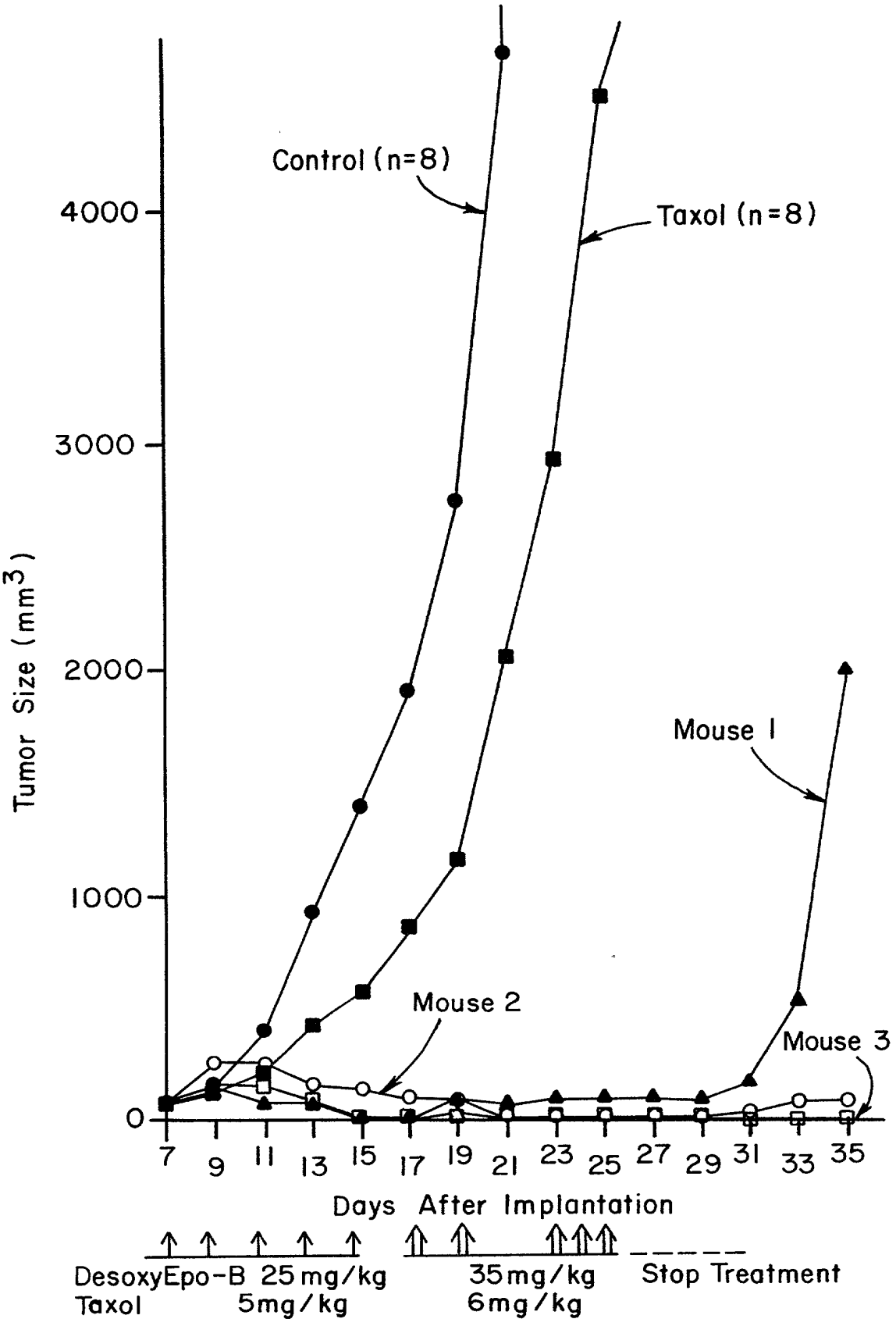

Control (n=8)
Taxol (n=8)
Mouse 1
Mouse 2
Mouse 3
Tumor Size (mm3)
4000
3000
2000
1000
0
7
9
11
13
15
17
19
21
23
25
27
29
31
33
35
Days After Implantation
DesoxyEpo-B 25 mg/kg
Taxol 5mg/kg
35mg/kg
6mg/kg
Stop Treatment

FIG. 46

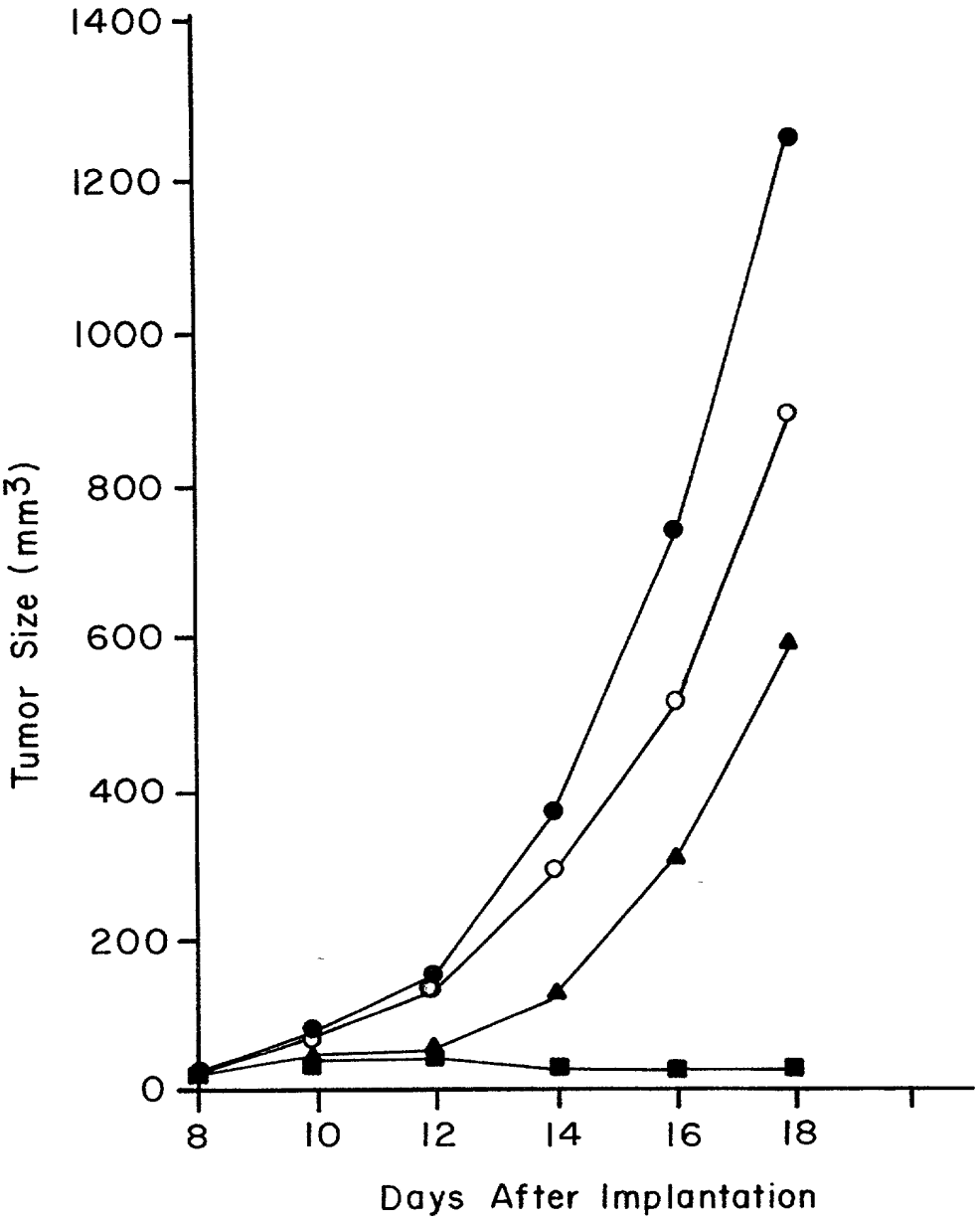

1400
1200
1000
800
600
400
200
0
Tumor Size (mm3)
8
10
12
14
16
18
Days After Implantation

FIG. 47

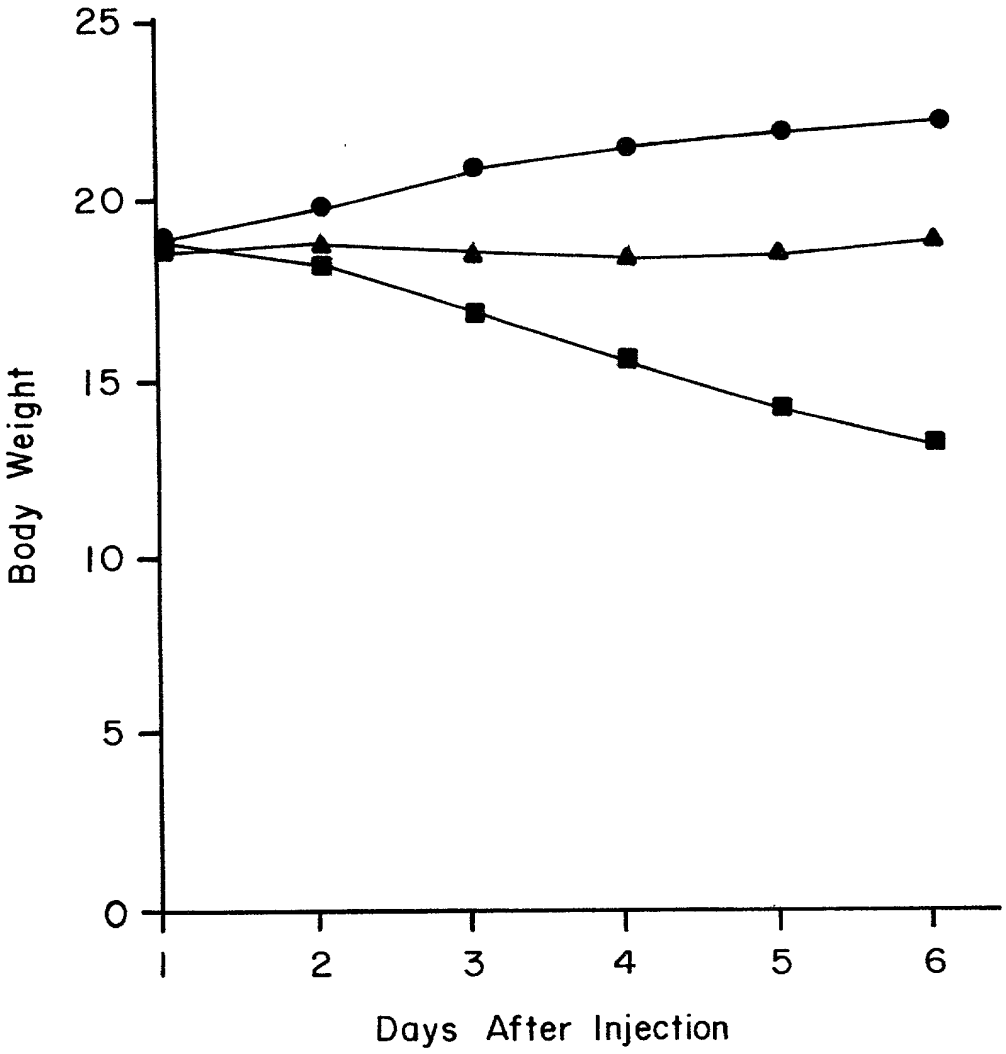


FIG. 48

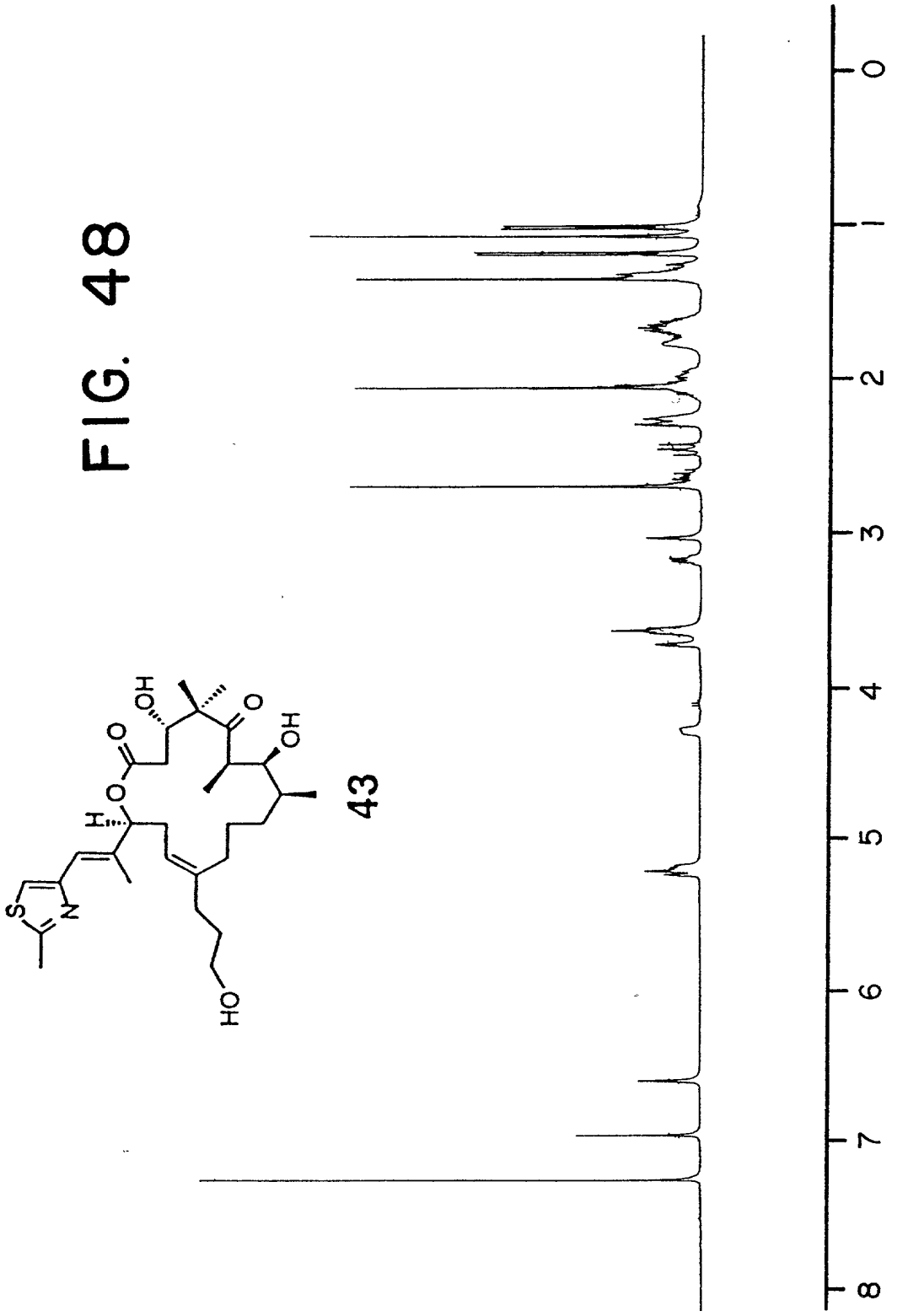
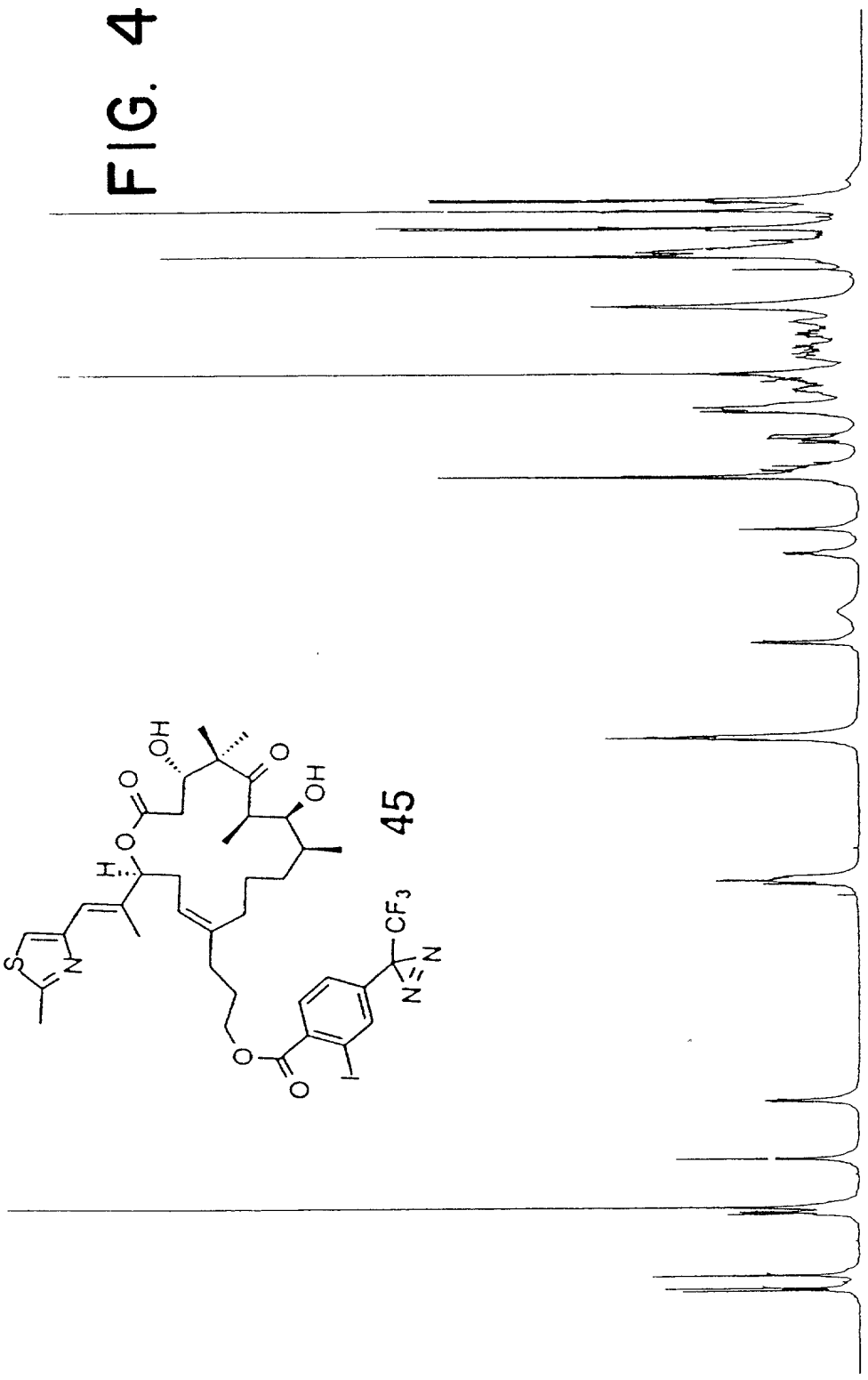


FIG. 49



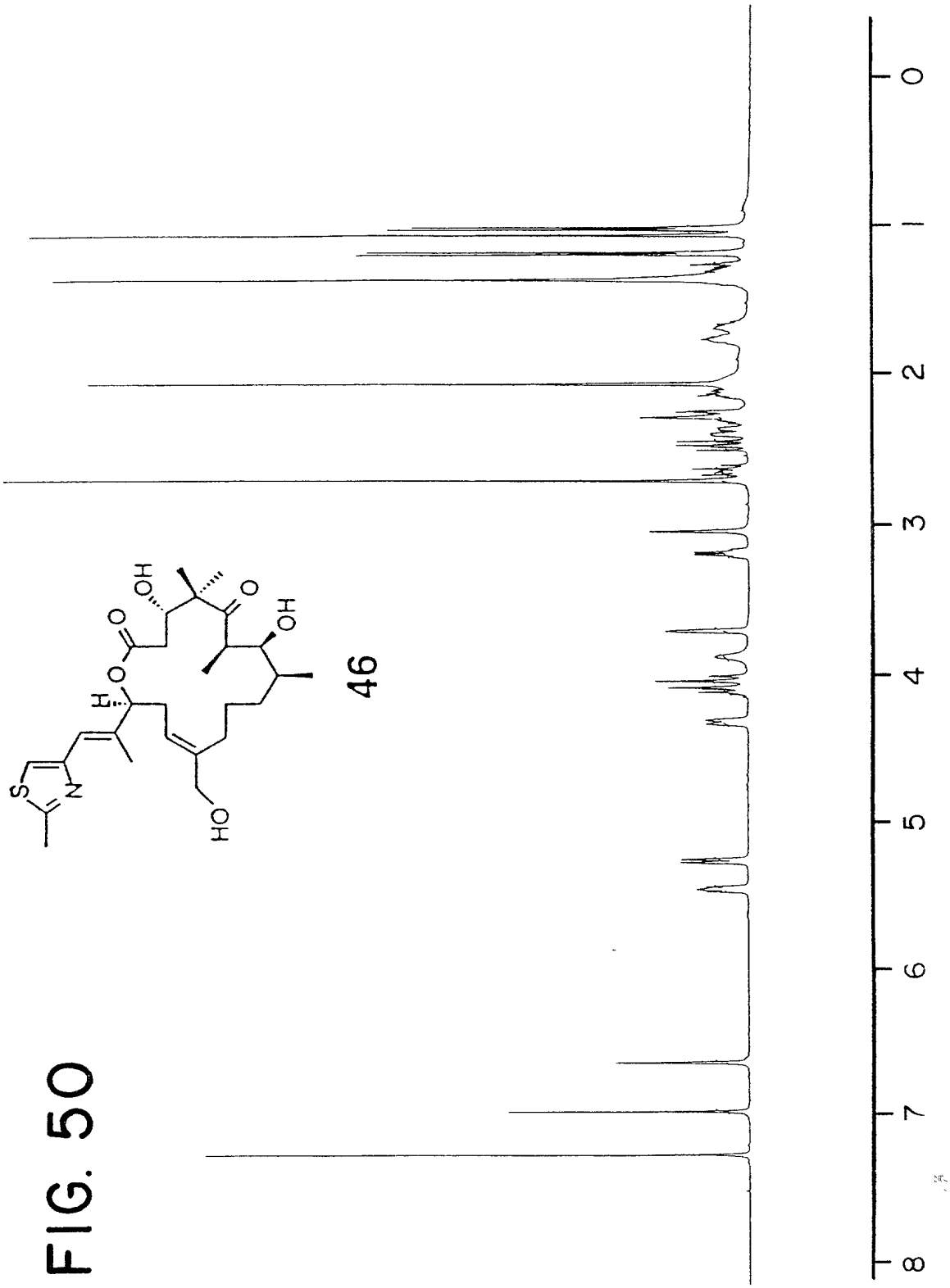


FIG. 50

FIG. 5I

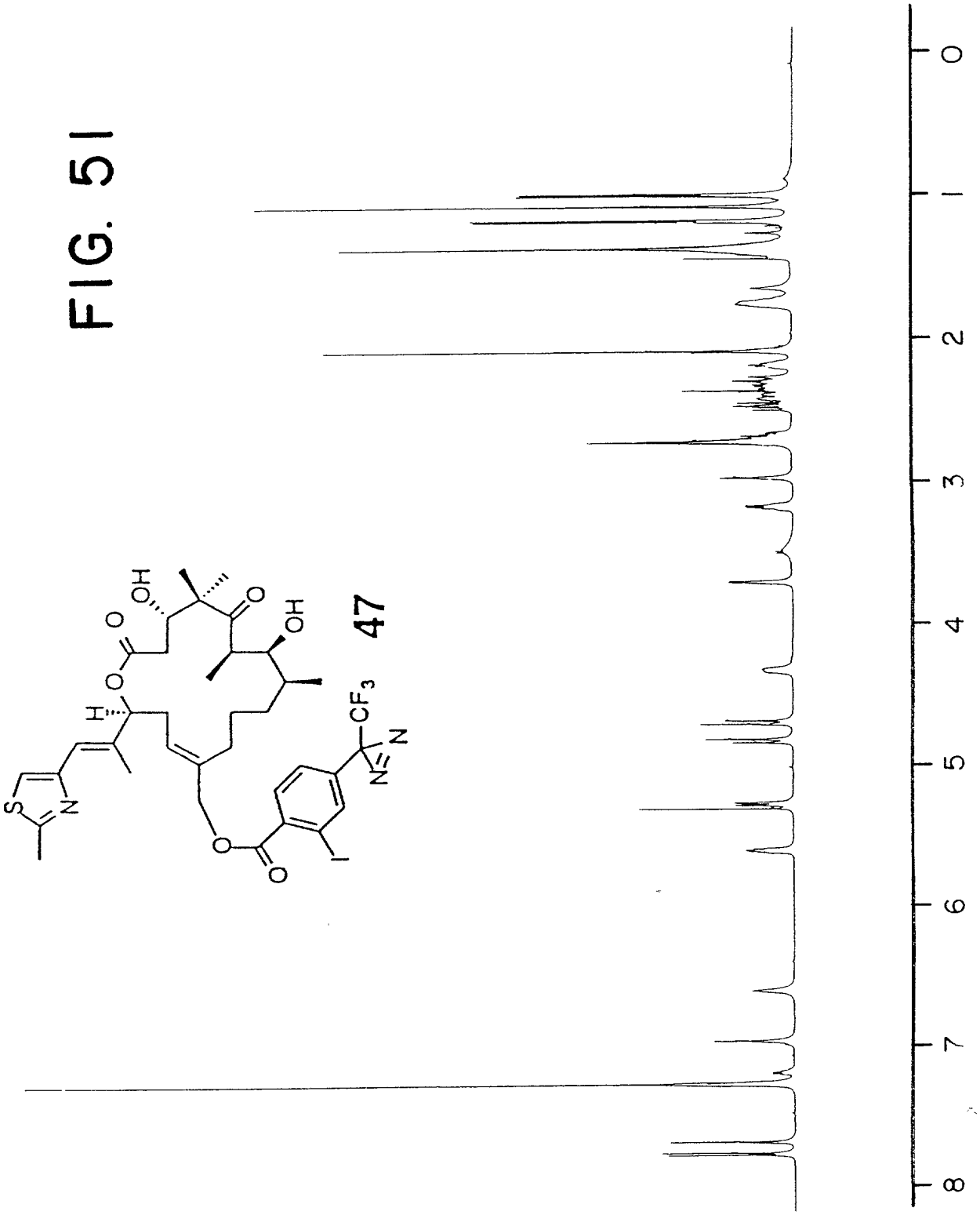


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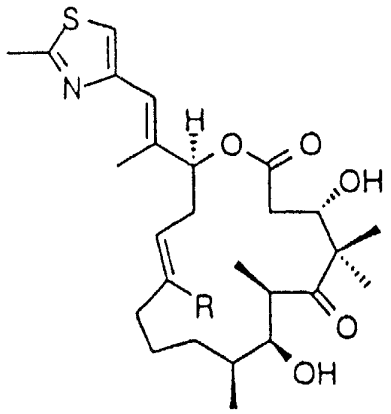
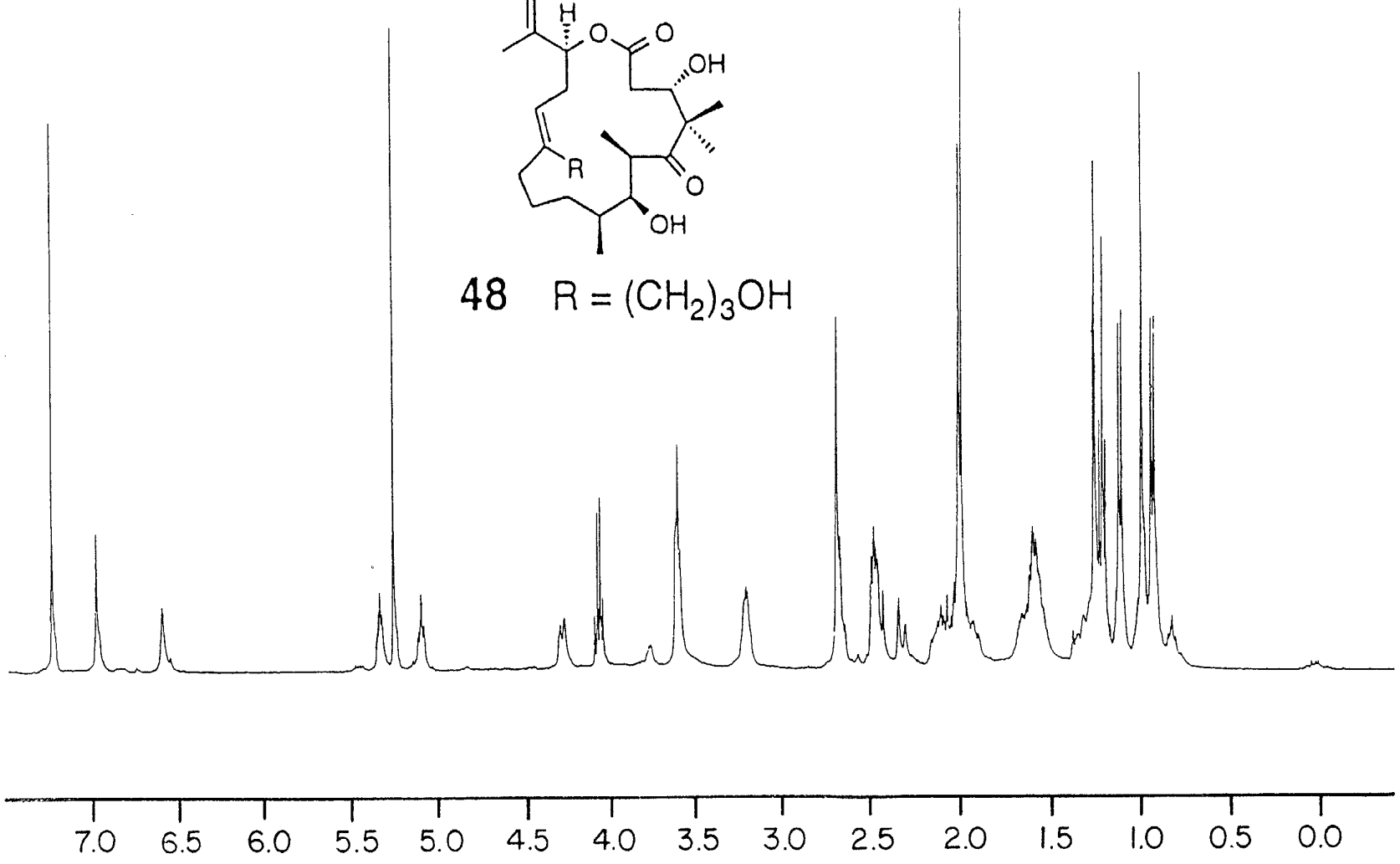
FIG. 52



48 R = $(CH_2)_3OH$